Early recognition of axial spondyloarthritis: imaging and genetic aspects

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‘Part of being optimistic is keeping one’s head pointed towards the sun, one’s feet moving forward’

Nelson Mandela, 1918-2013

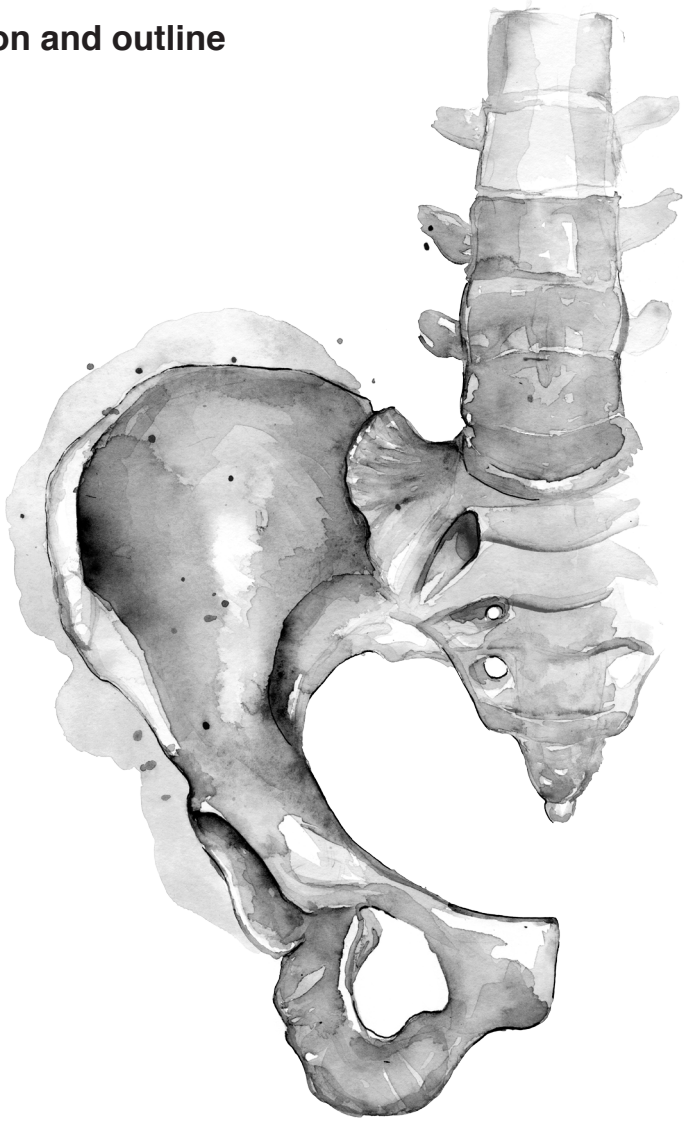
Aan mijn ouders

CONTENT

Part III: Genetic aspects in early axial spondyloarthritis

1

General introduction and outline



SPONDYLOARTHRITIS

Spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease. Until the 1960s, it was not identified as a separate disease entity but considered to be a subtype of seronegative arthritis. Fortunately, major advances have been made since then.

First, ankylosing spondylitis (AS) was recognized as a distinct disease entity with well-defined clinical and structural manifestations. Somewhat later in 1974, Moll et al. proposed for the first time to emphasize the interrelatedness of ankylosing spondylitis (AS) and several other conditions that had previously been described separately.[1] The umbrella term SpA was introduced and encompasses a group of clinically and genetically interrelated inflammatory rheumatic disorders, amongst others: AS, psoriatic arthritis (PsA) and arthritis associated with inflammatory bowel diseases (IBD). Patients with SpA features that do not fulfil criteria for one of the subgroups, were formerly known as undifferentiated SpA. The reason for this differentiation was both historical and practical, but all the subtypes share similar axial or peripheral articular manifestations and therefore each category does not represent a discrete disease entity.

Recent advances in the field accomplished that patients are nowadays distinguished according to their clinical presentation and distribution of joint involvement, in predominantly axial or peripheral disease.[2] Inflammation of the axial skeleton including the spine and sacroiliac (SI) joints is prominent in axial spondyloarthritis (axSpA) which is the main subject of this thesis. In peripheral spondyloarthritis (pSpA), inflammation is mainly located in peripheral joints. The advantages of this approach to describe patients with SpA are: a better characterization of the presenting disease and improved administration of treatment (since therapeutic approaches are different).

The estimated prevalence of SpA in the general population is 1-1.4%.[3,4] Although figures on the incidence and prevalence vary and are highly dependent on methodological differences between studies, the case definition used to define disease, HLA-B27 prevalence etcetera. SpA is associated with a significant burden of disease and young patients are affected. Around 80% of the patients develop first symptoms below 30 years of age (less than 5% of patients beyond 45 years of age).[5] The outcome of disease in terms of debilitating symptoms, decreased mobility, work-productivity and health-related quality of life (HR-QoL) has a major impact on patients in important stages in life.[6-9]

Early recognition of SpA is highly relevant. It is important to identify patients timely in order to treat early and possibly alter the disease course. Whereas adequate treatment was not available only years ago, the therapeutic arsenal has rapidly expanded since then. Non-steroidal anti-inflammatory drugs (NSAIDs) are still the recommended first-line drug treatment for patients with axSpA with pain and stiffness.[10-13] But the biologic era has revolutionized treatment options for patients refractory to first line treatment with impressive improvements.[14-19]

Unfortunately, the timely identification of patients is difficult and diagnostic delay is a major challenge in axSpA. The extended interval between symptom onset and diagnosis is reported to be 8-10 years (Figure 1).[20] AxSpA remains a relatively uncommon cause of a very common first symptom: 60-80% of the general population report back pain at some point in their lives. Also other factors play a role, which will be pointed out below. In general, the urge for an early recognition of axSpA provides the main rationale behind the different chapters described in this thesis.

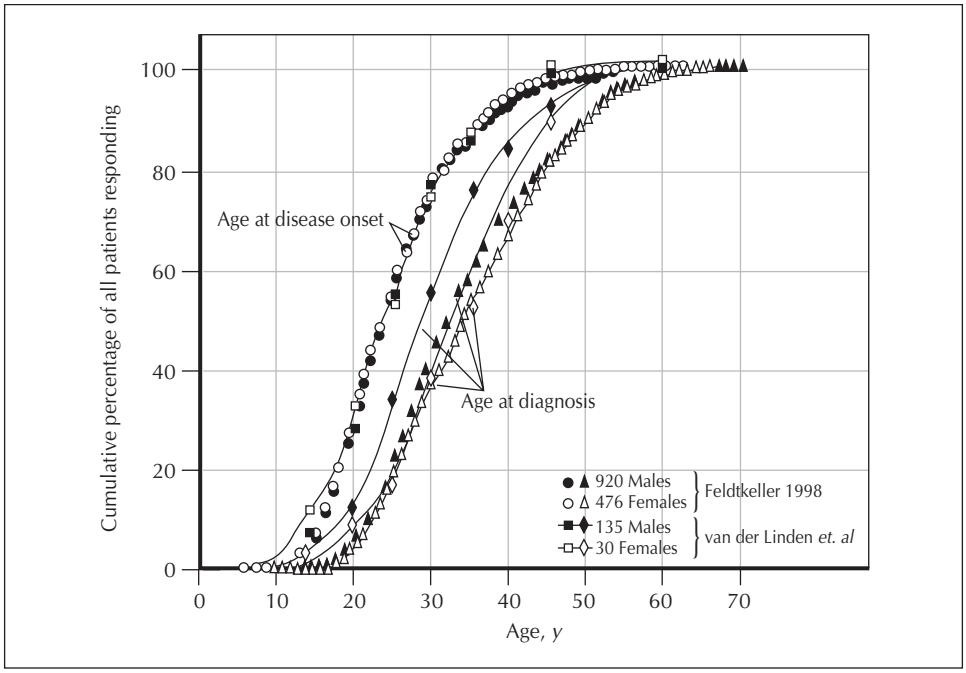


Figure 1: Cumulative distribution in age at symptom onset and diagnosis of SpA
Feldtkeller E, Bruckel J, Khan MA. Curr Opin Rheumatol 2000;12: 239-247.

EARLY RECOGNITION AND CLASSIFICATION CRITERIA

The exact aetiology of axSpA remains unknown and there is no single pathognomonic feature that distinguishes the disease from other conditions with similar symptoms. This is in contrast with other for example malignancies and infectious diseases where respectively histopathology findings and positive blood cultures are key findings in the diagnostic process.

The major clinical features which discriminate SpA from other forms of arthritis are the distribution and character of musculoskeletal manifestations and the co-existence of certain extra-articular manifestations. The most typical first presenting symptom of patients with axSpA is chronic back pain (CBP).[21,22] A combination of features is suggestive for an inflammatory aetiology: an insidious onset, onset of CBP before 40 years of age, improvement with exercise but not with rest and pain at night (with improvement at getting up). If four out of these five features are present CBP can be defined as inflammatory back pain (IBP) according to the Assessment of SpondyloArthritis international Society (ASAS) criteria.[23] IBP is present in 70-80% of patients with axSpA, but can also be seen in non-SpA patients, and therefore sensitivity and specificity are suboptimal.[24,25] Another characteristic of CBP in some axSpA patients is a good response to treatment with non- steroidal anti-inflammatory drugs (NSAIDs). Patients with back pain of other origin (e.g. overuse or degenerative changes, prevalence of degenerative changes was high in the SPACE cohort[26] may also experience alleviation of symptoms with NSAIDs, but marked improvement of pain within 24-48 hours after a full dose is relatively typical for SpA.[27] The natural history of axSpA is associated with a progressive impairment in spinal mobility over time. A restricted range of motion can be assessed by eleven tests during physical examination.[28-30] However, these tests are not very sensitive in the early detection of axSpA and subject to too large variation in normal subjects to be of diagnostic utility.[31]

When peripheral arthritis occurs in SpA it affects mainly (though not exclusively) the lower limbs (knees, ankles) typically in an asymmetrical pattern and is mostly mono-articular or oligo-articular of origin.[32,33] Enthesitis is a relatively specific SpA feature and refers to inflammation around the entheses: the site of insertion of ligaments, tendons, joint capsule or fascia to bone.[34] Typical locations are the insertion sites of the achilles tendon and plantar fascia ligament into the calcaneus, the ligamentous structures of the synchondrosis at the costovertebral joints and flexor and extensor tendon insertions at the humeral epicondyles.[32] These sites can be painful on palpation. Another characteristic feature of SpA is dactylitis, where in contrast to synovitis a diffuse inflammation and swelling of one digit (either foot or hand), also called a ‘sausage finger’ is present.

Next to musculoskeletal related symptoms, some extra-articular manifestations can be seen in patients with SpA: acute anterior uveitis, psoriasis and IBD. Acute anterior uveitis is characterized by abrupt, unilateral attacks of pain, photophobia, visual impairment and circumlimbial hyperaemia around the iris.[35,36] Around 50% of patients with acute recurrent unilateral anterior uveitis have SpA and in patients with AS there is a lifetime prevalence of uveitis of 30-40%.[36] Episodes of uveitis do not necessarily parallel the course of arthritis. The pooled prevalence of IBD among patients with AS was 6.8%, ulcerative colitis (UC) more common than Crohn's disease.[37] The dermatologic disorder psoriasis is present in up to 10% of patients with AS and it is more associated with peripheral joint involvement.[37,38]

Laboratory findings are useful in the diagnostic work-up of SpA, though there are no findings that are absolutely specific. Acute phase reactants including erythrocyte sedimentation rate (ESR) and levels of C-reactive protein (CRP) are increased in 35-50% of the axSpA patients.[5,39] Studies have shown that AS is associated with Human Leukocyte Antigen (HLA) B27 positivity and first-, second-, and third-degree relatives of patients with AS have markedly increased risk of developing disease.[40] The mode of inheritance is polygenic with multiplicative interaction among loci. More information on the association with HLA-B27 and other genetic risk factors can be found below.

Table 1: Overview of several axial SpA manifestations with accompanying test characteristics

Parameter	Sensitivity (%)	Specificity (%)	LR+	LR−
Inflammatory type of back pain[5 6]	75	76	3.1	0.33
Heel pain (enthesitis)	37	89	3.4	(0.71)†
Peripheral arthritis	40	90	4.0	(0.67)†
Dactylitis	18	96	4.5	(0.85)†
Iritis or anterior uveitis	22	97	7.3	(0.80)†
Psoriasis	10	96	2.5	(0.94)†
IBD	4	99	4.0	(0.97)†
Positive family history for axial SpA, reactive arthritis, psoriasis, IBD or anterior uveitis	32	95	6.4	0.72
Good response to NSAIDs	77	85	5.1	0.27
Raised acute-phase reactants (CRP/ESR)	50	80	2.5	0.63
HLA-B27‡	90	90	9.0	0.11
Sacroiliitis shown by magnetic resonance imaging	90	90	9.0	0.11

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NSAID, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis.
*LR+ = sensitivity/(1 − specificity); LR− = (1 − sensitivity)/specificity.
†As enthesitis, dactylitis, uveitis, peripheral arthritis, psoriasis and IBD may not be present at disease onset but may develop later, it is recommended to ignore a negative test result of these tests in an early state of possible axial SpA. The LR− of parameters, which should be ignored, are shown in brackets.
‡The figures for sensitivity and specificity of HLA-B27 refer to a European Caucasian population. In European Caucasian patients with psoriasis or IBD, a sensitivity of 50%, a specificity of 90%, an LR+ of 5.0 and an LR− of 0.56 for HLA-B27 should be applied. In other ethnic populations, sensitivity and specificity of HLA-B27 may be different, resulting in different LR+ and LR− (also discussed by Rudwaleit *et al*').

Rudwaleit M, Feldtkeller E, Sieper J. Ann Rheum Dis 2006;65: 1251-1252.

No formal diagnostic criteria are available for SpA. Instead, the expert opinion of the rheumatologist is leading. Diagnosis is generally based on a combination of the described SpA features in Table 1: symptoms obtained from medical history, physical examination and laboratory investigation, in addition to imaging findings (which will be addressed in the next part).[27] All these different characteristic features of the disease determine the likelihood of the

diagnosis SpA or axSpA; some are weighted more heavily than others (Table 1). The more features are present, the higher the probability of an axSpA diagnosis.

It is easy to understand that the diagnostic process for axSpA as described above will result in a heterogeneous group of patients. However, for research purposes (like cohort studies and clinical trials) the goal is to apply findings on a group-level. Therefore, more homogeneous groups of patients are warranted and this formed the basis of the development of classification criteria. Over time, several classification criteria sets have been developed. Most widely known are the, in 1984 developed, modified New York (mNY) criteria.[41] These are used for the classification of AS which is the most typical expression of axSpA. This criteria set combines the presence of clinical symptoms with radiographic sacroiliitis visible on conventional radiographs of the pelvis (sacroiliac joints). Radiographic sacroiliitis for the radiographic criterion of the mNY is defined as at least grade 2 bilateral sacroiliitis or grade 3 or 4 sacroiliitis unilaterally. A patient is classified as definite AS when in addition to fulfilment of the radiographic criterion, one of the following clinical criteria is met: low back pain and stiffness for more than three months with improvement during exercise but not during rest (1), limited motion of the lumbar spine in sagittal as well as frontal planes (2) or limited chest expansion compared to age- and sex-related normal values (3).

The mNY criteria are limited to axial features of the disease. Also important is the fact that radiographs are mainly useful in the assessment of advanced disease (which will be more extensively discussed below) and that not *all* patients will develop radiographic sacroiliitis. Overall, limitations of the mNY criteria initiated the development of the Amor criteria and ESSG criteria in the early 1990s.[32,42] These two criteria sets cover the whole spectrum of SpA and a broader range of manifestations of SpA are included, in comparison with the mNY criteria.

The Amor criteria consist of a list of symptoms, none of which is required to classify a patient as SpA. Points (between 1 and 3) are assigned to the different symptoms and in total at least 6 points are necessary for classification.[42] In contrast to the Amor criteria, the ESSG criteria uses entry criteria by means of a mandatory presence of inflammatory back pain (IBP) or peripheral arthritis.[32] According to the ESSG criteria, patients with at least one of the entry criteria in combination with one minor criterion are classified as having SpA. The Amor and ESSG criteria cover the whole spectrum of SpA, but they are not able to differentiate axial from peripheral disease, which is important as stated earlier. There are also drawbacks with respect to sensitivity; Magnetic Resonance (MR) imaging is a more sensitive tool than conventional radiographs to detect early sacroiliitis, changes are visible even years before the development of radiographic sacroiliitis (which will be further explained in Part 2). In 2009, a group of experts in the ASAS proposed two new classification criteria sets for SpA

(Figure 2): one for axSpA[39], one for peripheral SpA.[33]

According to the ASAS classification criteria for axSpA (ASAS axSpA) application of the criteria can take place when a patient suffers from chronic back pain for minimal three months with age at onset before 45 years (entry criterion). A patient can be classified as axSpA when fulfilment is met via (minimally) one of the two arms: the imaging and/or clinical arm.

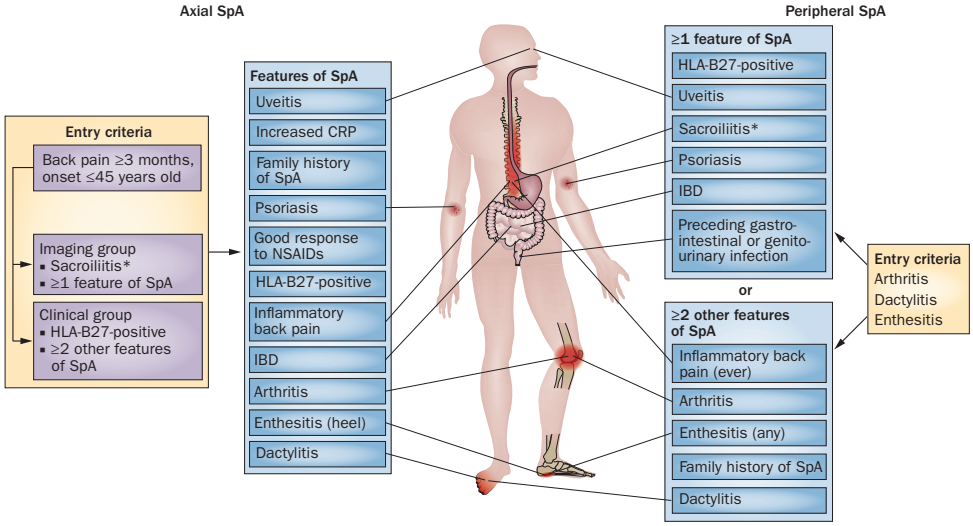


Figure 2: ASAS classification criteria for axial and peripheral SpA
ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs; HLA-B27-positive, human leukocyte antigen B27-positive; IBD, inflammatory bowel disease; SpA, spondyloarthritis.
Van Tubergen A. Nat Rev Rheumatol 2015;11: 110-118.

In the imaging arm, patients can be classified as axSpA if one SpA feature is present in addition to either radiographic sacroiliitis (mNY criteria) or active inflammation detected by MRI highly suggestive of sacroiliitis.[39] To fulfil the clinical criteria, the patient should be HLA-B27 positive and have at least two other SpA-associated features.

The classification criteria for peripheral SpA can be applied in patients with currently peripheral manifestations only. To fulfil these criteria, a patient must have arthritis, dactylitis or enthesitis in combination with either at least one other SpA feature (Table 1, Figure 2).[33] All three different criteria sets described above have shared SpA features and this overlap is visualized in Figure 3.

The ASAS criteria have been implemented worldwide. Validation was performed in different cohorts. When tested against the expert's diagnosis ('gold' standard) the criteria set performed well. In the original validation study, the following test characteristics were seen:

a sensitivity of 82.9% and a specificity of 84.4% (overall); sensitivity of 66.2% and specificity of 97.3% (imaging arm alone) and a sensitivity of 56.6% (sensitivity) and 83.3% (specificity) for the clinical arm alone.[39] The ASAS criteria reflect the current perception of what SpA looks like (so-called gestalt) better than the ESSG and Amor criteria.

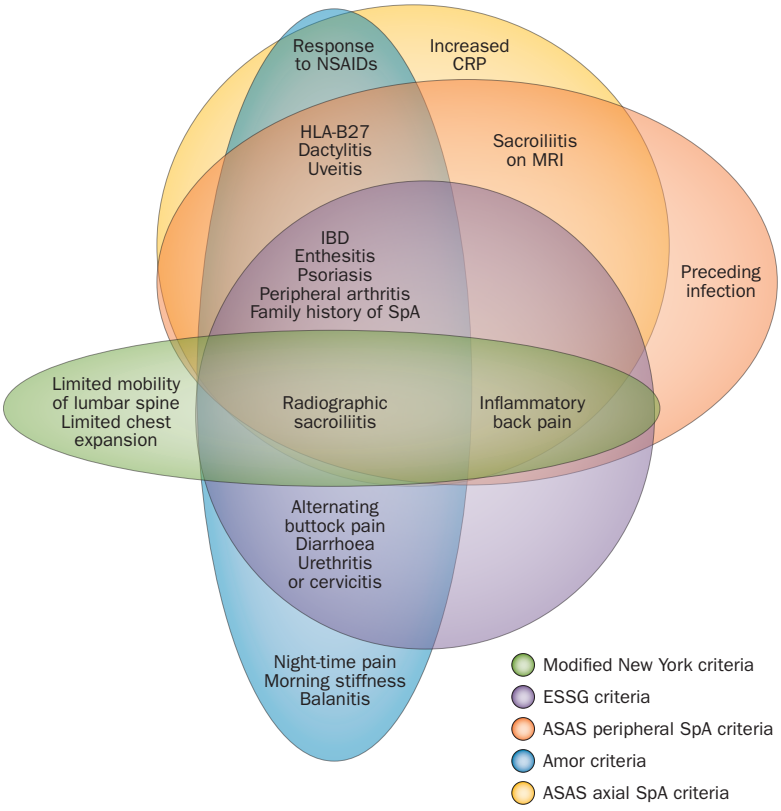


Figure 3: Venn diagram showing overlap of features of the various SpA classification criteria sets
ASAS, Assessment of SpondyloArthritis international Society; axial SpA, axial spondyloarthritis; ESSG, European Spondyloarthropathy Study Group; CRP, C-reactive protein; HLA-B27, human leukocyte antigen B27; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease.
Van Tubergen A. Nat Rev Rheumatol 2015;11: 110-118.

THE USE OF IMAGING (MRI) IN EARLY AXIAL SPONDYLOARTHRITIS

As mentioned before sacroiliitis is the hallmark of axSpA and therefore sacroiliac joint imaging plays a pivotal role in both the diagnostic work-up and the classification of axSpA. For many years, conventional radiographic imaging of the pelvis was the only imaging modality of choice.

Over time it became apparent that in early axSpA patients radiographic abnormalities can be absent. Structural changes might only become apparent several years after the onset of symptoms, which severely contributes to diagnostic delay. Moreover, it has been shown that it is very difficult to reliably detect and grade sacroiliitis on conventional radiographs. Substantial intra- and interobserver variability exists and this is not ameliorated by training.[43,44]

Since MRI shows high anatomic detail in addition to bone marrow changes, early inflammatory lesions in the sacroiliac (SI) joints can be identified.[45,46] It has become evident that inflammatory lesions can be visible on MRI years before radiographic structural changes are detectable. Therefore, in the early disease course MRI may detect acute inflammatory lesions in the absence of radiographic sacroiliitis. A short screening protocol is introduced using two sequences: a coronal oblique T1-weighted (turbo spin echo) TSE sequence and short tau inversion recovery (STIR) sequence. Consequently, MRI has become an important additional instrument in the early detection of axSpA and was included in the modified Berlin Algorithm (a helpful tool in axSpA diagnosis.[47] The term non-radiographic axSpA (nr-axSpA) was introduced to differentiate patients with AS (radiographic axSpA, r-axSpA). (Figure 4). It is important to emphasize that a substantial proportion of the patients with nr-axSpA will progress to r-axSpA, but not *all* nr-axSpA patients will develop r-axSpA. The speed of this shift is still unclear and only a few predisposing factors are identified yet.

In 2009, a group of ASAS experts in the field of axSpA set up specific criteria to define a so-called 'positive MRI'.[45] The presence of definite subchondral bone marrow edema (BME)/ osteitis highly suggestive of sacroiliitis is mandatory. On the other hand, the presence of synovitis, capsulitis, or enthesitis only, without subchondral BME/osteitis, is compatible with but *not* sufficient for defining a positive MRI. Furthermore, to mark an MRI-SI as positive, one inflammatory lesion should be visible on at least two consecutive coronal-oblique slices or more lesions should be present on a single slice.

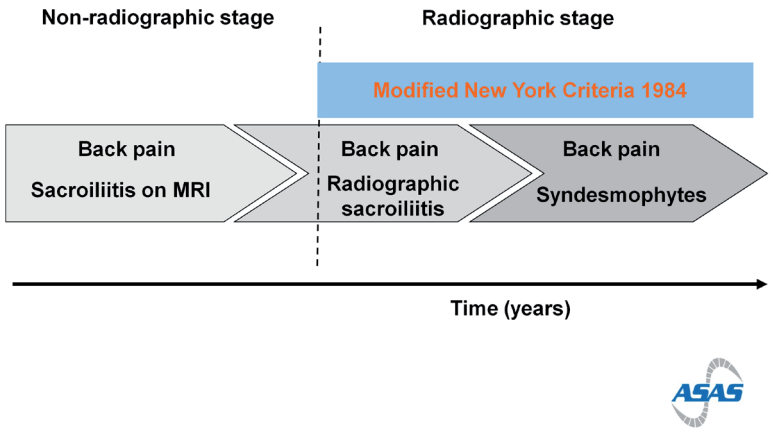


Figure 4: Unifying concept of axial SpA showing schematically the transition from early to late disease
Rudwaleit M, Khan MA, Sieper J. Arthritis Rheum 2005;52: 1000-1008.

GENETIC ASPECTS IN EARLY AXIAL SPONDYLOARTHRITIS

The aetiology of SpA is largely unknown but both genetic and environmental factors play a role. Despite the above described heterogeneous character of clinical manifestations, genetic similarities among patients are seen.[48] Family aggregation studies have shown that genetic risk factors contribute 80-90% of the susceptibility to AS; with high concordance rates in monozygotic (50-75%) and dizygotic twins (15%), which are markedly higher than the prevalence in the population at large.[49,50]

The major genetic risk factor currently known is HLA-B27, a major histocompatibility (MHC) class I molecule. The association between HLA-B27 and AS was recognized 40 years ago and is by far the strongest association with the disease.[51,52] The overall contribution of HLA-B27 to AS heritability is estimated at 23.3% and only 5-6% of HLA-B27 positive people in the general population will develop SpA.[53] This led to the hypothesis that HLA-B27 by itself is not sufficient for development of the disease, suggesting the contribution of additional genes.

Different single nucleotide polymorphisms (SNPs) have been identified via candidate gene studies. More recently, due to technologic improvements large genome-wide association studies (GWAS) have been carried out, which has led to the identification of many new genetic risk factors. Currently, over 30 genetic loci have been described to be operative in AS susceptibility.[54]

DATABASES USED IN THIS THESIS

To accomplish the objectives of this thesis (presented below), data from three different cohort studies were used. A summary of these studies is provided below:

SPACE

SPondyloArthritis Caught Early (SPACE) is a multinational cohort study aiming at an early diagnosis of axSpA as well as identifying factors that are predictive for progression of the disease.[55] Unlike the cohorts stated below this is an *on-going* cohort study founded in the Leiden University Medical Center (LUMC) in the Netherlands. But inclusion rapidly expanded to other countries (Norway, Italy, Sweden) and other participating centres in the Netherlands (Amsterdam, Gouda). Since the initiation of the cohort in 2009, more than 600 patients are included. Patients aged 16 years and older are included in case of chronic back pain for more than 3 months, but less than two years with an onset before the age of 45 years. Patients were not included if other painful conditions not related to SpA could interfere with the evaluation.

DESIR

Baseline data from the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort were also used. DESIR is a prospective, longitudinal cohort study in which patients aged 18-50 years with inflammatory back pain (IBP) suggestive of axSpA are included.[56] The presence of IBP according to the Calin or Berlin criteria[57,58] and a back pain duration of more than three months and less than three years was required for inclusion. Besides the mandatory presence of IBP, a patient was only included if the rheumatologist responsible for the enrolment had a level of confidence about the diagnosis of SpA of at least 5 (0-10 scale; where 0 is not confident and 10 is very confident). All patients included in the cohort have the French nationality, but the study has a multi-centre character due to the fact that inclusion took place in 25 different centres across France. The cohort is aiming at a 10-year follow-up, though only baseline data were used for this thesis. In contrary to the SPACE-cohort which

has an on-going inclusion, DESIR is a closed cohort of 708 patients and inclusion stopped after the goal of 700 patients was reached (inclusion between January 2007-April 2010).

In general, the SPACE cohort has important similarities to DESIR, though an important difference is that in DESIR patients with IBP are included, whereas SPACE includes patients with chronic back pain not necessarily IBP. Furthermore, in DESIR the presence of an axSpA diagnosis is at least probable whereas this is not the case in SPACE.

COMOSPA

Under the umbrella of ASAS, the COMOrbidities in SPondyloArthritis (COMOSPA) study was initiated. This is an international, observational study with a cross-sectional design in which patients diagnosed with SpA (according to the treating rheumatologist) were included.[59] The primary aim of this study was to evaluate the prevalence of comorbidities and risk factors in different countries worldwide and to evaluate the gap between available recommendations and daily practice for management of these comorbidities. The worldwide character of this study makes it unique: inclusion took place in 22 countries from five different regions across the world: Asia, North Africa, Latin America, North America, Central Europe and Western Europe. This interesting feature of the study paved the way for the investigation of other research questions.

OUTLINE OF THE THESIS

Classification criteria are frequently used to include patients in clinical trials and cohort studies. Validation was predominantly done in restricted patient populations. In **chapter 2** we compare the performance of various SpA classification criteria sets in a worldwide population of patients (the above described COMOSPA study). By testing the fulfilment of the different criteria sets, we investigate similarities and phenotypical overlap in patients that were worldwide diagnosed with SpA. It is relevant to investigate if rheumatologists worldwide diagnose patients with a similar clinical picture of disease. Since there is debate in the literature among SpA-experts in the field concerning the relevance and validity of the clinical arm of the axSpA-criteria, disease characteristics of patients fulfilling the imaging and clinical arm are also compared.

Due to the heterogeneous character of the disease and the high prevalence of CBP, the diagnostic process of axSpA can be challenging for rheumatologists and other physicians. The modified Berlin algorithm (Figure 5) may facilitate clinicians in establishing an early diagnosis of axSpA with greater confidence. A downside of the algorithm is that conventional

radiographs are advised in all referred patients with CBP of a certain duration and onset <45 years of age, regardless of the presence of other SpA features. But it is currently unclear if additional investigations (besides conventional radiographs, also sacroiliac joint MRI and HLA-B27 testing) are necessary to perform in all patients. This is of particular importance in the subgroup of patients with only zero or one SpA feature after clinical examination and measurement of acute phase reactants in serum. Therefore, in **chapter 3**, we investigate in this subgroup of patients the incremental value of HLA-B27 testing and both sacroiliac joint imaging modalities: conventional radiographs and MRI of the sacroiliac joints.

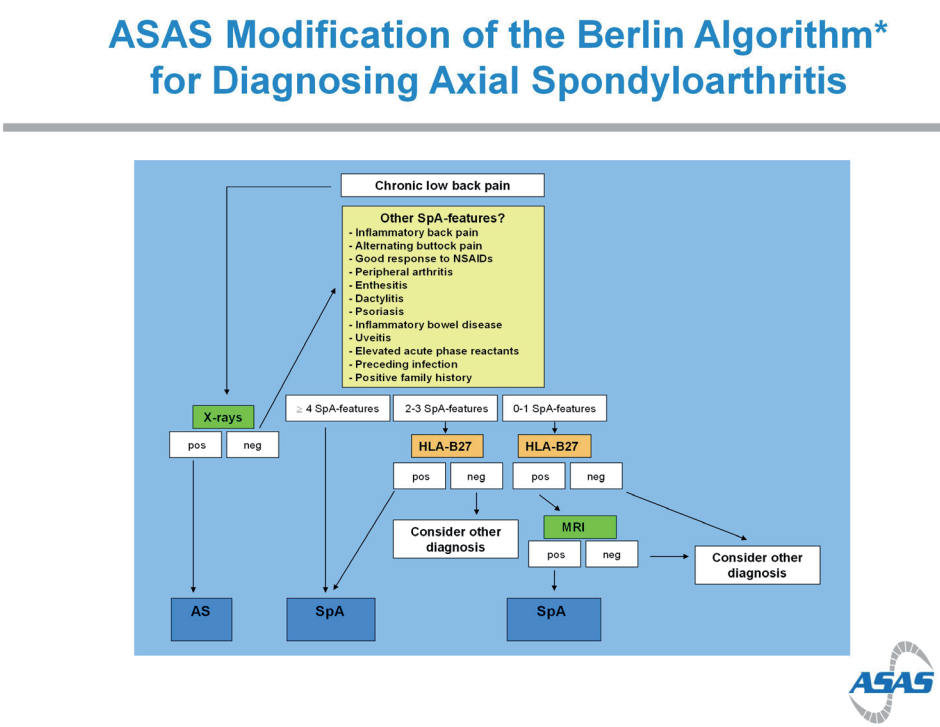


Figure 5: Modified Berlin algorithm.
AS, ankylosing spondylitis; SpA, spondyloarthritis; pos, positive; neg, negative; MRI, magnetic resonance imaging; X-rays, conventional radiographs; HLA-B27, human leukocyte antigen B27; NSAIDs, non-steroidal anti-inflammatory drugs.
Van den Berg R, de Hooge M, Rudwaleit M, et al. Ann Rheum Dis 2013;72:1646-1653.

Both conventional radiographs and MRI of the sacroiliac joints are commonly used imaging modalities in the detection of sacroiliiitis. Over the last decade, major advances in sacroiliac joint imaging have led to a better understanding of its role in the early detection of axSpA. To provide an overview of these recent advances in sacroiliac joint imaging, a systematic literature review was performed and results are described in **chapter 4**. The aim of this review was mainly two-fold: to summarize studies evaluating the reliability of conventional

radiographs of the sacroiliac joints and to wrap-up evidence on the diagnostic value of MRI of the sacroiliac joints in SpA.

In 2009 the ASAS definition for a positive MRI (described above) was introduced. Since only 30-50% of axSpA patients have active sacroiliitis on MRI, it was questioned whether the wording of the definition for a positive MRI was still appropriate. Therefore, a consensus exercise (**chapter 5**) was initiated in which recently published data on this respect were examined and discussed. Four questions were relevant: how does the current ASAS definition for a positive MRI perform? (1) Do we need an update of the existing definition (2) Do we need to add MRI features of structural changes of the SI-joint (3) Do we need to include features of the spine in the definition (4).

An important conclusion of the above described consensus exercise was that the additional value of using structural lesions in the ASAS axSpA criteria needs to be further investigated. Besides inflammatory lesions, on MRI structural lesions (fatty lesions, erosions, sclerosis and ankylosis) are visible on MRI. Therefore, MRI has the great potential for the assessment of both active inflammatory lesions and structural damage by means of one single imaging technique. The EULAR recommendations[60] for the use of imaging in the diagnosis and management of axSpA in clinical practice, advocated to take structural lesions into account in the diagnostic process. However, the utility of adding structural lesions seen on MRI of the sacroiliac joints to the imaging criterion of the ASAS axSpA classification is yet unknown. This was investigated in two different cohorts (DESIR and SPACE) in **chapter 6** and **chapter 7**. An even more drastic approach would be the replacement of radiographic sacroiliitis by structural lesions in the ASAS axSpA criteria and this was also assessed.

The increased attention for MRI of the sacroiliac SI joints in the diagnostic work-up of axSpA also leads to new opportunities and research questions. We know that in contrast to radiographic abnormalities, inflammatory, bone marrow edema (BME) lesions are volatile and can change over time. But not much data is present on the repeated performance of MRI-SI in the diagnostic process and how BME develops over time: it can become quiescent after an initial phase of activity or newly positive MRIs can be seen. This could have implications, for example the question if repeating MRI is necessary in the diagnostic process. If an MRI is completely normal at the first investigation, but there is still a persistent clinical suspicion of SpA, should the MRI be repeated? If so, after what period of follow-up and in which patients? These questions are all subject of study in **chapter 8**.

As described above, genetic factors influence AS susceptibility. While HLA-B27 is known to be the major risk factor, interaction with other genes is suggested. HLA-B*4001 (an allele that corresponds to HLA-B60 at the serological or protein level) is identified as another

genetic risk factor for AS. In three independent AS populations, it was investigated if HLA-B*4001 was increased in HLA-B27 positive AS patients.[61-63] The combined high risk AS genotype HLA-B27+/HLA-B*4001+ was found to have a high specificity in three different AS populations (sensitivity varying between 10.1%-18.7% and specificities: 98.7-99.7%) and epistatic interaction was also found in one other study.[61-63]

However, the high specificity of the HLA-B27+/HLA-B*4001+ genotype has only been investigated in late stage AS patients. In **chapter 9** we study the prevalence of the HLA-B27+/HLA-B*4001+ genotype in the SPACE and DESIR cohort and two matched populations of healthy controls; evaluate the additional value of testing in the detection of early axSpA.

Finally, in **chapter 10** the findings of this thesis are summarized and discussed. A Dutch summary is provided in **chapter 11**.

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The performance of different classification criteria sets for spondyloarthritis in the worldwide ASAS-COMOSPA study

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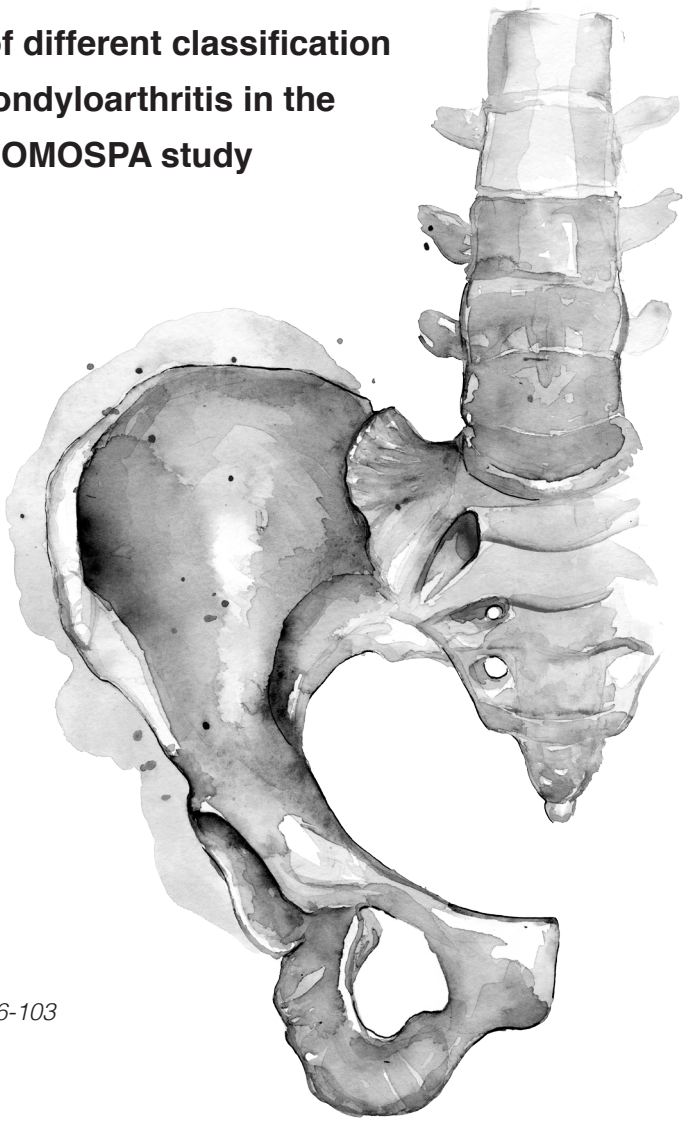

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ABSTRACT

Objective

In this study, we sought to compare the performance of spondyloarthritis (SpA) classification criteria sets in an international SpA cohort with patients included from five continents around the world.

Methods

Data from the (ASAS) COMOrbidities in SPondyloArthritis (ASAS-COMOSPA) study were used. ASAS-COMOSPA is a multinational, cross-sectional study with consecutive patients diagnosed with SpA by rheumatologists worldwide. Patients were classified according to the European Spondyloarthropathy Study Group (ESSG), modified European Spondyloarthropathy Study Group (mESSG), Amor, modified Amor, Assessment of SpondyloArthritis international Society (ASAS) axial Spondyloarthritis (axSpA), ASAS peripheral spondyloarthritis (pSpA) and CIASsification criteria for Psoriatic Arthritis (CASPAR) criteria. Overlap between the classification criteria sets was assessed for patients with and without back pain. Furthermore, patients fulfilling different arms of the ASAS axSpA criteria (imaging arm, clinical arm, both arms) were compared on the presence of SpA features.

Results

A total of 3942 patients (5 continents, 26 countries) were included. The mean age was 43.6 years, 65.0% were male, 56.2% were human leucocyte antigen B27-positive and 64.4% had radiographic sacroiliitis (based on modified New York criteria). Of the patients, 85.5% were classified by the ASAS SpA criteria (87.7% ASAS axSpA,12.3% ASAS pSpA). Fulfilment of the Amor, ESSG and CASPAR criteria was present in 83.3%, 88.4% and 21.6% of patients, respectively. Of the patients with back pain (n = 3227), most were classified by all three of Amor, ESSG and ASAS axSpA criteria (71.4%). Patients fulfilling the imaging arm and the clinical arm of the ASAS axSpA criteria had similar presentations of SpA features. In patients without back pain, overlap between classification criteria sets was seen, although to a lesser extent.

Conclusions

Most patients with a clinical diagnosis of axSpA in the worldwide ASAS-COMOSPA study fulfil several classification criteria sets, and a substantial overlap between different criteria sets is seen, which suggests a high level of credibility of the criteria. Large inter-regional differences in the fulfilment of classification criteria were not found. Patients fulfilling the clinical arm were remarkably similar to patients fulfilling the imaging arm with respect to the presence of most SpA features.

INTRODUCTION

Spondyloarthritis (SpA) encompasses a group of interrelated rheumatic conditions: ankylosing spondylitis (AS), including earlier forms of the disease that do not yet exhibit definitive structural damage on radiographs; psoriatic arthritis (PsA); arthritis associated with inflammatory bowel disease (IBD); and reactive arthritis.[1] Because SpA may have a heterogeneous presentation, a correct diagnosis is challenging. Rheumatologists make a diagnosis on the basis of what they have been taught during rheumatology training. The 'art of diagnosing' starts with a list of potential differential diagnoses, from among which the trained clinician deducts the most appropriate disease based upon the recognition of the 'Gestalt' and exclusion of other diagnoses.

Classification serves a completely different purpose, and several classification criteria sets of SpA are available. These classification criteria should be applied only in patients who have been diagnosed with SpA by a rheumatologist, and they cannot be used as a check box to be ticked in order to make the diagnosis. But the components of classification criteria may remind the clinician of the clinical picture of the disease. Different criteria sets put an emphasis on different features, and we do not know to what extent different criteria sets have penetrated different parts of the world. Therefore, we do not know which sets have influenced clinicians in particular regions most or to what extent these various sets of criteria describe more or less similar patients. Consequently, we do not know if rheumatologists around the world diagnose patients with a similar clinical picture of the disease.

The European Spondyloarthropathy Study Group (ESSG) criteria and the Amor criteria were developed to classify patients with SpA as a whole.[2,3] In clinical practice, rheumatologists tend to distinguish patients with SpA according to their primary clinical presentation as patients with predominantly axial or predominantly peripheral complaints (with some overlap between these subtypes). The Assessment of SpondyloArthritis international Society (ASAS) has developed new criteria to better accommodate this distinction.[4,5] These criteria sets can classify patients with predominantly axial symptoms as having axial spondyloarthritis (axSpA) and patients with predominantly peripheral symptoms as having peripheral spondyloarthritis (pSpA). The ASAS axSpA criteria consist of two arms: the imaging arm classifies patients who have sacroiliitis visualised on conventional radiographs and/or bone marrow oedema on magnetic resonance imaging (MRI), and the clinical arm classifies patients with normal imaging results. In 2006, a specific classification criteria set for PsA was developed, known as the ClASsification criteria for Psoriatic ARthritis (CASPAR).[6]

Classification criteria are used to include patients in clinical trials, cohort studies and other types of research. These criteria are frequently validated in restricted patient populations.

We took the opportunity to investigate if rheumatologists worldwide diagnosed similar types of patients as having SpA by testing if patients fulfil similar criteria sets in the Assessment of SpondyloArthritis international Society COMOrbidities in SPondyloArthritis (ASAS-COMOSPA) study. Our assumption was that the more criteria sets a patient fulfils, the higher the likelihood that a patient with a diagnosis of SpA truly has SpA. The ASAS-COMOSPA study provides a unique opportunity to investigate this research question because it is, to our knowledge, the first observational study with such a large, worldwide population of patients with SpA, with axial and/or peripheral symptoms included.[7]

METHODS

Study population

The ASAS-COMOSPA study is an observational, cross-sectional, multicentre study which has been introduced elsewhere.[7] Participating rheumatologists were asked to include consecutive patients with a diagnosis of SpA from routine care. These patients had to fulfil the ASAS axSpA or pSpA criteria, but fulfilment of the ASAS criteria was not checked before inclusion. All information required to judge the fulfilment of various criteria sets, including the ASAS criteria, was collected in a random order (not grouped by criteria set) in the case report form.

Patients from 26 participating countries in 6 regions across the world (Western Europe, Central Europe, North America, Latin America, North Africa and Asia) were included. Western Europe was represented by Belgium, France, Germany, Hungary, Italy, the Netherlands, Portugal, Spain and the United Kingdom. Poland, Russia, Turkey and Ukraine were grouped into Central Europe. North America encompasses Canada and the United States, and Argentina, Brazil, Colombia and Mexico were summarized as Latin America. North Africa comprised Egypt and Morocco. China, Japan, Korea, Singapore and Taiwan were grouped and referred to as Asia. Approval by the local medical ethics committees, as well as written informed consent from all patients, was obtained before inclusion.

Classification criteria

Patients were classified according to the following criteria sets: ESSG, Amor, ASAS SpA, ASAS axSpA, ASAS pSpA, imaging arm of ASAS axSpA, clinical arm of ASAS axSpA and CASPAR criteria.[8] The presence of either inflammatory back pain (IBP) or peripheral arthritis is a mandatory entry criterion of the ESSG criteria. According to the ESSG criteria, patients with at least one of the entry criteria in combination with one other minor criterion, such as enthesitis or psoriasis, are classified as having SpA.[2] Human leukocyte antigen B27 (HLA-B27) is not incorporated in this criteria set. The Amor criteria include a list of features

with different weights, none of which is essential to classify a patient as having SpA, but a classification of SpA depends on the sum of weights.[3] Because patients in the COMOSPA study were not asked about the presence of balanitis, night pain and buttock pain, these items have not been taken into account, and therefore patients cannot collect points on these items in the Amor and ESSG criteria. The ESSG and Amor criteria were developed before MRI became widely available. In the present analysis, we also investigated the possibility of including inflammatory findings on MRI (ASAS definition)[9] as a feature in both the ESSG and Amor criteria, resulting in the modified Amor (mAmor) and modified European Spondyloarthropathy Study Group (mESSG) criteria.

The ASAS axSpA criteria consist of two arms, the imaging arm and the clinical arm, and can be applied only to patients with back pain of ≥3 months' duration and an age of onset <45 years.[10] In patients with sacroiliitis visualised on pelvic radiographs or MRI, at least one other SpA feature should be present in order to be classified as axSpA according to the imaging arm.[4] In HLA-B27-positive patients, at least two other additional SpA features should be present in order to be classified as axSpA according to the clinical arm.[4] In patients without current back pain but with current peripheral manifestations, the classification for peripheral SpA can be applied. If a patient satisfies the entry criterion (current arthritis, enthesitis or dactylitis), the patient should have at least one other SpA feature if this is a specific SpA feature or at least two SpA features for less specific features.[5] Altogether, when current back pain (as defined above) is the presenting symptom, the ASAS axSpA criteria should be applied. If arthritis/enthesitis/dactylitis is the presenting symptom, the peripheral SpA criteria should be applied. Together, these two sets form the ASAS SpA criteria.

A separate classification criteria set has been developed for PsA: the CASPAR criteria.[6] To meet the CASPAR criteria, the stem of the criteria demands first the presence of inflammatory articular disease and a score of at least 3 points derived from the presence of features such as skin psoriasis, dactylitis, nail lesions or juxta-articular bone formation visualised on radiographs (each feature is assigned a certain number of points). All above-described criteria sets are depicted in the supplementary material: Supplementary Tables 1-4.

Data analysis

Disease characteristics were described using descriptive statistics. The fulfilment of classification criteria was calculated for the cohort as a whole and thereafter per region. Subsequently, overlap between the different classification criteria was investigated and presented in Venn diagrams. This was done for patients with back pain and patients without back pain separately. Next, we looked in detail at the fulfilment of the ASAS axSpA criteria, comparing patients fulfilling only the clinical arm, patients fulfilling only the imaging arm and patients fulfilling both the clinical and imaging arms with regard to demographics and the

presence of SpA features. Information on HLA-B27 must be available to be able to classify patients in the 'imaging arm-only' group, and information on imaging must be available to be able to classify patients in the 'clinical arm-only' group. IBM SPSS Statistics version 20.0 software (IBM, Armonk, NY, USA) was used for statistical analysis.

RESULTS

In total, 3984 patients were included in the COMOSPA study, with a mean number of SpA features of 5.5 (SD 1.8). The most common missing items were MRI of the sacroiliac joints (missing in 1951 patients), the presence of juxta-articular bone formation (missing in 999 patients) and HLA-B27 status (missing in 882 patients). There were 251 patients (6.4%) for whom both sacroiliac joint MRI and radiographs were not performed and 180 patients (4.6%) for whom HLA-B27 in addition was missing.

Table 1: Baseline characteristics

	Total number n = 3942	Based on available data	Number of patients with missing items
Age (years), mean ±SD	43.6 (13.9)		0
Male, n (%)	2563 (65.0%)		0
HLA-B27 positive, n (%)	2217 (56.2%)	72.0%	882
IBP, n (%)	3219 (81.7%)		52
Morning stiffness, n (%)	2497 (63.3%)		22
Enthesitis, n (%)	1354 (34.3%)		0
Dactylitis, n (%)	610 (15.5%)		3
Psoriasis, n (%)	843 (21.4%)		0
Uveitis, n (%)	771 (19.6%)		0
Peripheral Arthritis, n (%)	2424 (61.5%)		0
IBD, n (%)	209 (5.3%)		0
Positive family history, n (%)	1475 (37.4%)		117
Good response to NSAIDs, n (%)	2433 (61.7%)	77.5%	803
Elevated CRP, n (%)	2109 (53.5%)	57.7%	287
Preceding infection, n (%)	271 (6.9%)		74
Sacroiliitis radiograph (mNY), n (%)	2539 (64.4%)	70.0%	341
Sacroiliitis MRI, n (%)	1326 (33.6%)	65.7%	1951
Negative rheumatoid factor, n (%)	3177 (80.6%)	94.8%	613
Psoriatic nail dystrophy, n (%)	460 (11.7%)		28
Juxta-articular bone formation, n (%)	526 (13.3%)	17.7%	999

HLA-B27, human leukocyte antigen B27; IBP, inflammatory back pain (according to the Assessment of SpondyloArthritis international Society (ASAS) definition;); IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; CRP, C-reactive protein; mNY, modified New York criteria, MRI, magnetic resonance imaging.

On the other hand, information on extra-articular manifestations was missing in none of the cases. Arbitrarily, a maximum of 6 missing items (total number of 18 items) per patient was accepted. Patients with 7 or more missing items (n = 42) were left out of the analysis, which brings the total number of patients for this analysis to 3942. To define SpA features as present or absent, in order to apply the classification criteria, missing items were regarded as absent.

Demographics and disease characteristics are depicted in Table 1. Patients had a mean age of 44 years, and 65% were male. In the total cohort (patients with available data), HLA-B27 positivity was seen in 56% (73.0%) of the patients, and 54% (57.7%) had an elevated C-reactive protein level. Regarding the presence of sacroiliitis visualised on imaging, 64% (70.0%) presented with sacroiliitis seen on radiographs and 34% (94.8%) with sacroiliitis seen on MRI.

Fulfilment of classification criteria

Most (92.6%) of the 3942 patients fulfilled the mESSG criteria. Fulfilment of Amor, mAmor, ESSG and ASAS criteria was all above 80% (Table 2). A minority (12.3%) of the patients fulfilled the ASAS pSpA criteria, whereas 21.6% of the patients fulfilled the CASPAR criteria. We emphasise that the criteria were applied to all patients; only the patients with seven or more missing values were left out, and missing items were regarded as absent.

Table 2: Fulfilment of classification criteria

Classification criteria	Patients that fulfil the classification criteria, n (%)
Amor	3282 (83.3%)
mAmor	3454 (87.6%)
ESSG	3485 (88.4%)
mESSG	3652 (92.6%)
ASAS SpA total	3370 (85.5%)
ASAS axial SpA	2955 (87.7%)
Both arms (imaging & clinical)	1737 (58.8%)
mNY+	976 (56.2%)
MRI+	169 (9.7%)
Both	592 (34.1%)
Imaging arm only	984 (33.3%)
mNY+	539 (54.8%)
MRI+	245 (24.9%)
Both	200 (20.3%)
Clinical arm only	234 (7.9%)
ASAS peripheral SpA *no current back pain*	415 (12.3%)
CASPAR	852 (21.6%)

mAmor, modified Amor; ESSG, European Spondylarthropathy Study Group; mESSG, modified European Spondyloarthropathy Study Group; ASAS, Assessment of SpondyloArthritis international Society; SpA, spondyloarthritis; mNY, modified New York; MRI, magnetic resonance imaging; CASPAR, CIASsification criteria for Psoriatic Arthritis.

Most patients (n = 1507) were included in Western Europe (85 centres from 26 countries), followed by 1073 patients in Asia, 438 patients in Central Europe, 337 patients in Latin America, 337 patients in North Africa and 239 patients in North America. Regional differences in fulfilment of classification criteria are depicted in Table 3. When we looked in detail at the ASAS SpA criteria, we found that in Central Europe, 84% of the patients fulfilled the ASAS axSpA criteria (ASAS peripheral criteria 5.3%), whereas in contrast, in North America, 51% of the patients fulfilled the axSpA criteria (ASAS peripheral criteria 22.6%). In both Asia and Central Europe, a small minority of the patients fulfilled the ASAS pSpA criteria, and the axial complaints were by far the predominant symptoms. A relatively high percentage of patients fulfilled the CASPAR criteria in North America compared with the other regions. Less pronounced regional differences were seen regarding criteria sets that cover the whole spectrum of SpA, namely the Amor and ESSG criteria.

Overlap in classification criteria

Venn diagrams representing the overlap between the different criteria sets are shown in Figures 1 and 2. Figure 1 reveals that the majority of the patients with back pain were classified by all three criteria sets: Amor, ESSG and ASAS axSpA criteria (n = 2392 [74.1%]).

Most patients who fulfilled two criteria sets fulfilled both the ASAS axSpA criteria and the ESSG criteria (n = 268 [8.3%]). Few patients fulfilled only one criteria set. Most of the patients who were picked up by one criteria set only were classified by the ASAS axSpA criteria (n = 179 [5.5%] compared with 1.3% by the ESSG criteria only and 0.2% by the Amor criteria only). The major overlap of the criteria points to the typical clinical pattern of SpA the included patients have.

Regarding the patients without current back pain (peripheral complaints), again substantial overlap between the criteria was seen (ASAS pSpA, Amor, ESSG, CASPAR) (Figure 2). Most of the patients fulfilled all four criteria sets (n = 224 [31.3%]). Subsequently, 125 patients (17.5%) fulfilled all criteria, except those for PsA-specific CASPAR criteria, which is not surprising, because the CASPAR criteria are focussed on the clinical disease PsA and not on other forms of pSpA. Only six patients (0.8%) fulfilled only the CASPAR criteria, and only four patients (0.6%) fulfilled only the ASAS pSpA criteria. Regarding overlap between the different criteria sets in the different regions, the same trends were seen, and no substantial interregional differences were found (data not shown).

Table 3: Regional differences in fulfilment of classification criteria

	Number of patients included	**Amor criteria** Patients fulfilling n (%)	**mAmor criteria** Patients fulfilling n (%)	**ESSG criteria** Patients fulfilling n (%)	**mESSG criteria** Patients fulfilling n (%)	**ASAS SpA total** Patients fulfilling n (%)	**ASAS axSpA** Patients fulfilling n (%)	**ASAS pSpA** Patients fulfilling n (%)	**CASPAR criteria** Patients fulfilling n (%)
Western Europe	1507	1242 (82.4%)	1333 (88.5%)	1335 (88.6%)	1433 (95.1%)	1305 (86.6%)	1149 (76.2%)	156 (10.4%)	388 (25.7%)
Central Europe	438	342 (78.1%)	364 (83.1%)	402 (91.8%)	419 (95.7%)	391 (89.3%)	368 (84.0%)	23 (5.3%)	32 (7.3%)
North America	239	203 (84.9%)	205 (85.8%)	219 (91.6%)	219 (91.6%)	176 (73.6%)	122 (51.0%)	54 (22.6%)	120 (50.2%)
Latin America	348	290 (83.3%)	307 (88.2%)	314 (90.2%)	326 (93.7%)	280 (80.5%)	239 (68.7%)	41 (11.8%)	93 (26.7%)
North Africa	337	300 (89.0%)	310 (92.0%)	316 (93.8%)	324 (96.1%)	308 (91.4%)	260 (77.2%)	48 (14.2%)	94 (27.9%)
Asia	1073	905 (84.3%)	935 (87.1%)	899 (83.8%)	931 (86.8%)	910 (84.8%)	817 (76.1%)	93 (8.7%)	125 (11.6%)

Percentages relate to number of patients of that specific region
mAmor, modified Amor; ESSG, European Spondylarthropathy Study Group; mESSG, modified European Spondyloarthropathy Study Group; ASAS, Assessment of SpondyloArthritis international Society; SpA, spondyloarthritis; axSpA, axial spondyloarthritis; pSpA, peripheral spondyloarthritis; CASPAR, CIASsification criteria for Psoriatic Arthritis.

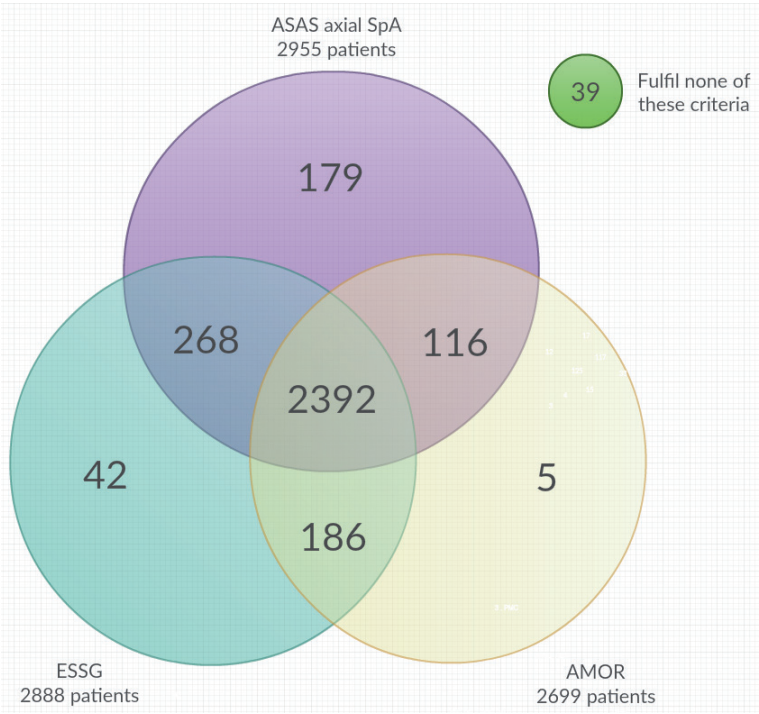

Figure 1: Overlap between ESSG, AMOR, and axSpA criteria in patients with current back pain (n=3227)
ESSG, European Spondylarthropathy Study Group; ASAS, Assessment of SpondyloArthritis international Society; axial SpA, axial spondyloarthritis.

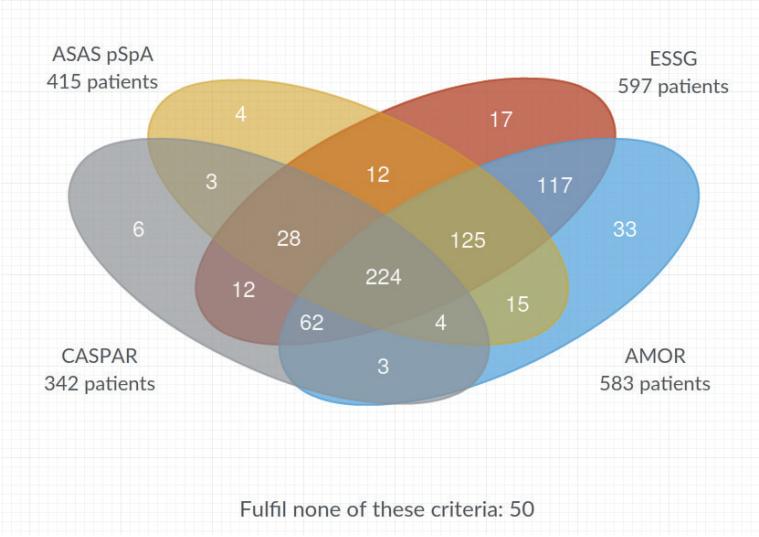

Figure 2: Overlap between the ESSG, AMOR, CASPAR, and pSpA criteria in patients without current back pain (n=715)
ESSG, European Spondylarthropathy Study Group; ASAS, Assessment of SpondyloArthritis international Society; pSpA, peripheral SpondyloArthritis; CASPAR, ClASsification criteria for Psoriatic Arthritis.

Table 4: Comparison between the imaging arm and clinical arm of the ASAS axSpA criteria, with the required presence of HLA-B27 and imaging

	Imaging arm (%), HLA-B27 always available		Clinical arm alone (%) Imaging always available
	HLA-B27+ N total = 1746	HLA-B27- N total = 546	N total = 98
Age	40.3 (13.0)	42.7 (13.0)	42.8 (13.0)
Sex (male)	1294 (74.1%)	275 (50.4%)	52 (53.1)
IBP	1639 (93.3%)	529 (96.9%)	87 (88.8%)
Peripheral arthritis	904 (51.8%)	302 (55.3%)	57 (58.2%)
Psoriasis	147 (8.4%)	105 (19.2%)	14 (14.3%)
Uveitis	453 (25.9%)	49 (9.0%)	27 (27.6%)
Enthesitis	563 (32.2%)	164 (30.0%)	44 (44.9%)
Dactylitis	137 (7.8%)	55 (10.1%)	17 (17.3%)
IBD	73 (4.2%)	46 (8.4%)	6 (6.1%)
Positive family history	669 (38.3%)	166 (30.4%)	52 (53.1%)
Good response to NSAIDs	1180 (67.6%)	265 (48.5%)	64 (65.3%)
Elevated CRP	1094 (62.7%)	256 (46.9%)	41 (41.8%)

HLA-B27, human leukocyte antigen B27; IBP, inflammatory back pain; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; CRP, C-reactive protein.

Comparison between patients fulfilling the ASAS imaging arm split by presence of HLA-B27 and the clinical arm only

Disease characteristics of patients fulfilling the imaging arm or the clinical arm only are depicted in Table 4. In addition, characteristics of patients fulfilling the imaging arm are presented on the basis of the presence or absence of HLA-B27. Only patients who have data available on HLA-B27 and imaging are included in Table 4. There were more male patients in the HLA-B27-positive imaging arm (74.1%) than in the HLA-B27-negative imaging arm (50.4%) and the clinical arm (53.1%). Psoriasis was seen more frequently in the group of HLA-B27-negative patients fulfilling the imaging arm. On the contrary, enthesitis and dactylitis were relatively more common in the patients who fulfilled only the clinical arm. A positive family history was also more frequently seen in the clinical arm than in the imaging arm (independent of HLA-B27 status).

DISCUSSION

Appropriate diagnostic criteria for axSpA and pSpA do not exist and, in the absence of an unequivocal gold standard, will never be developed, but various classification criteria are available. These classification criteria have in common that they have been developed using the external standard 'expert opinion'. But expert opinion is not an equivocal and homogeneous construct and may potentially integrate different pictures of the disease SpA.

The present study reveals that, in our cohort, most patients diagnosed as having SpA fulfilled multiple classification criteria sets, which adds to the credibility of the construct of SpA as a recognizable entity. Although the substantial overlap between the different criteria sets for patients with both axial and with peripheral symptoms could be expected, the fact that different criteria sets have been developed for different target populations (e.g., the ESSG, focussed on the whole concept of SpA; the ASAS axSpA criteria for patients with SpA axial symptoms) could have precluded overlap in different regions of the world. In the present study, we have shown that the significant overlap was consistent all over the world, thus suggesting that rheumatologists worldwide use similar 'pictures' of what SpA is. In other words, they operationalise the construct of SpA approximately similarly. In addition, the huge overlap (e.g., 74.1% of the patients fulfilled all three criteria sets, and only 7.6% fulfilled one set only) confirms that the criteria for SpA are highly credible.

As mentioned already, large interregional differences in the fulfilment of classification criteria were not found. This is remarkable in the light of all genetic and environmental differences, as well as differences in resources and health care systems around the world. In fact, it appears that the clinical picture—and consequently the diagnosis—of SpA is remarkably homogeneous around the world, despite all possible differences in, for example, genetic background, prevalence and medical training.

Of course, there were some notable differences. The most important one was that more patients with PsA and fewer patients with axial disease were included in North America than in other regions. We do not think this reflects a true difference in the prevalence of the different subtypes of the disease. This is supported by a recent systematic review that pooled population prevalence estimates for SpA, AS and PsA in geographic areas.[11] The prevalence of both the axial and peripheral subtypes was, on average, comparable in North America to other parts of the world. More likely, the difference could be due to local factors, such as a difference in areas of interest of the doctors including patients or referral centres for a certain disease. One reason may be the perception of PsA as belonging to SpA or not. It is well known that some rheumatologists view PsA as a separate entity and others view PsA as a subtype of SpA. Apparently, more doctors in North America than in other parts of the

world consider patients with PsA as having SpA.

Regarding the inclusion criteria of the study, doctors were required to include patients with SpA only if they thought the patient would fulfil the ASAS SpA criteria (either peripheral or axial). However, fulfilment of the ASAS criteria was not formally checked before inclusion, as described in the Methods section above. When analysing the data, it became clear that only 85.5% of the patients actually did fulfil the ASAS SpA criteria, ranging from 73.6% in North America to 91.4% in North Africa. This implies that the large majority of patients with SpA are indeed covered by the criteria, pointing to high sensitivity but also indicating that doctors diagnose SpA in patients who do not fulfil the ASAS criteria. However, we would like to make a critical comment which relates to a limitation of the present study. The fact that rheumatologists were initially asked to include ASAS SpA patients (although fulfilment of the ASAS criteria was not met in all patients) could very well have led to an 'a priori' high percentage of ASAS classification criteria fulfilment. This could have led to an overestimation of performance of sensitivity of the criteria.

The ASAS classification criteria were developed in recent history. The criteria were validated in an international study of more than 600 patients with chronic back pain of unknown origin. In the ASAS study population, the ASAS criteria compared favourably with other previously established criteria sets with regard to sensitivity and specificity. In our study, if patients with axial symptoms were picked up by one criteria set only, of all sets tested, the ASAS axSpA criteria were most sensitive (although the others performed well, too). The latter could be due to the fact that the ASAS-COMOSPA study is not a cohort of early disease (as reflected by 65% modified New York criteria positivity). Prior studies have shown that performances of, for example, ESSG and Amor criteria in early disease were (slightly) worse than the ASAS criteria.[12] A more likely explanation is that the rheumatologists were asked to include patients fulfilling the ASAS criteria.

Although the imaging arm of the ASAS classification criteria is broadly recognized as highly specific, there has been debate on the validity of the clinical arm of the ASAS criteria, which has not been well received by different national and international health care systems. In the literature, it has been argued that patients fulfilling only the clinical arm of the ASAS axSpA criteria should not be considered as having 'true axSpA'. A reason why the clinical arm of the ASAS axSpA criteria has been developed is that MRI is not universally available. In our cohort, in which a large proportion of patients did not undergo MRI, our results demonstrate the value of the clinical arm of the ASAS criteria for scientific research. We found that patients fulfilling the clinical arm were remarkably similar to patients fulfilling the imaging arm with respect to the presence of many SpA features.

Strengths of the study are the multi-national cohort and the large number of patients included, which is unique, to our knowledge. Unfortunately, no control group was available, and therefore true specificity of the different classification criteria sets could not be calculated. Another limitation of the study is the relatively high number of missing values, especially when it comes to key items such as HLA-B27 and MRI. Unfortunately, this is a direct consequence of normal clinical practice: If sufficient information has been collected to make a diagnosis, further testing is often not performed (e.g., to save expenses).

We can conclude that, despite the heterogeneous character and varying prevalence of SpA as a disease across the world, similar patients are identified as having SpA by rheumatologists worldwide. Moreover, patients with the diagnosis of SpA usually fulfil multiple criteria sets, providing validity to the criteria, including the relatively new ASAS SpA criteria as well as to the concept of SpA. We emphasize that classification criteria for SpA were developed for use in epidemiological and clinical research and are not suitable for use as diagnostic tools in clinical practice.

CONCLUSIONS

Most patients diagnosed with SpA by rheumatologists in five continents across the world fulfilled multiple classification criteria sets. To our knowledge, this is the first study confirming the validity of the ASAS axSpA criteria in a large, worldwide population of patients. Patients fulfilling the clinical and/or imaging arms of the ASAS axSpA criteria have comparable SpA features.

For the first time, to our knowledge, the performance of the various SpA classification criteria sets is assessed in a worldwide setting with a very large number of patients included from five different continents. We also took the opportunity to phenotypically compare patients fulfilling the different arms of the ASAS axSpA criteria in terms of demographics and presence of SpA features, among others.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Amor Criteria

Amor criteria[3]	
Items	Score
Clinical symptoms/history	
Pain at night (spine) or morning stiffness	1
Asymmetrical oligoarthritis	2
Gluteal (buttock) pain (any) or alternating gluteal pain	1 or 2
Sausage like digit or toe (dactylitis)	2
Enthesitis (heel)	2
Uveitis	2
Urethritis/cervicitis within 1 month before onset of arthritis	1
Diarrhea within 1 month before onset of arthritis	1
Psoriasis, balanitis or inflammatory bowel disease	1
X-rays	
Sacroiliitis (grade 2 bilaterally or grade 3 unilaterally)	3
Genetic background	
HLA-B27 positive or positive family history for AS, ReA, uveitis, psoriasis or inflammatory bowel disease	2
Good response to NSAIDs	
NSAIDs show a good response within 48 hours, or relapse within 48 hours after NSAIDs are stopped	2
	At least 6 points are necessary

HLA-B27, human leukocyte antigen B27; AS, ankylosing spondylitis; ReA, reactive arthritis; NSAIDs, non-steroidal anti-inflammatory drugs.

Supplementary Table 2: ESSG criteria

European Spondyloarthropathy Study Group (ESSG) criteria[2]		
Inflammatory back pain	**OR**	Synovitis *Asymmetric or Predominantly in the lower limbs*
	plus one of the following:	
	Enthesitis (heel)	
	Positive family history	
	Psoriasis	
	Crohn's disease, colitis ulcerosa	
	Urethritis/cervicitis or acute diarrhea within one month before arthritis	
	Buttock pain (alternating between right and left gluteal areas)	
	Sacroiliitis	

Supplementary Table 3a: ASAS axSpA criteria

ASAS Classification Criteria for Axial Spondyloarthritis (SpA)[4]		
In patients with ≥3 months back pain and age at onset <45 years		
Sacroiliitis on imaging** **plus ≥1 SpA feature**	**OR**	HLA-B27 **plus ≥2 SpA features**
	SpA features:	
	Inflammatory back pain	
	Arthritis	
	Enthesitis (heel)	
	Uveitis	
	Dactylitis	
	Psoriasis	
	Crohn's/colitis	
	Good response to NSAIDs	
	Family history for SpA	
	HLA-B27	
	Elevated CRP	

**Sacroiliitis on imaging:
- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- Definite radiographic sacroiliitis according to the modified New York criteria

SpA, spondyloarthritis; SpA feature, spondyloarthritis feature; NSAIDs, non-steroidal anti-inflammatory drugs; HLA-B27, human leukocyte antigen B27; CRP, C-reactive protein.

Supplementary Table 3b: ASAS pSpA criteria

ASAS Classification Criteria for Peripheral Spondyloarthritis (SpA)[5]		
Arthritis or enthesitis or dactylitis		
plus		
≥1 SpA feature	**OR**	**≥2 SpA features**
Uveitis		Arthritis
Psoriasis		Enthesitis
Crohn's/colitis		Dactylitis
Preceding infection		IBP (ever)
HLA-B27		Family history for SpA
Sacroiliitis on imaging		

Peripheral arthritis usually predominantly lower limbs and/or asymmetric arthritis
Enthesitis: clinically assessed
Dactylitis: clinically assessed
IBP: inflammatory back pain
ASAS, Assessment of SpondyloArthritis international Society; SpA, spondyloarthritis; SpA-feature, spondyloarthritis feature; IBP, inflammatory back pain.

Supplementary Table 4: CASPAR criteria

Classification of Psoriatic Arthritis: CASPAR criteria[6] ClASsification criteria for Psoriatic ARthritis To meet the CASPAR criteria for PsA, a patient must have inflammatory articular disease (joint, bone, spine, or entheseal) and score ≥3 points based on these categories	
	Points
Evidence of psoriasis	
Current psoriasis	2 or
Personal history of psoriasis	1 or
Family history of psoriasis	1
Psoriatic nail dystrophy Pitting, onycholysis, hyperkeratosis	1
Negative result for rheumatoid factor	1
Dactylitis	
Current swelling of an entire digit	1 or
History of dactylitis	1
Radiologic evidence of juxta-articular new bone formation: ill-defined ossification near joint margins on plain x-rays of hand/foot	1

2

3

Are additional tests needed to rule out axial spondyloarthritis in patients ages 16 - 45 years with short-duration chronic back pain and maximally one spondyloarthritis feature?

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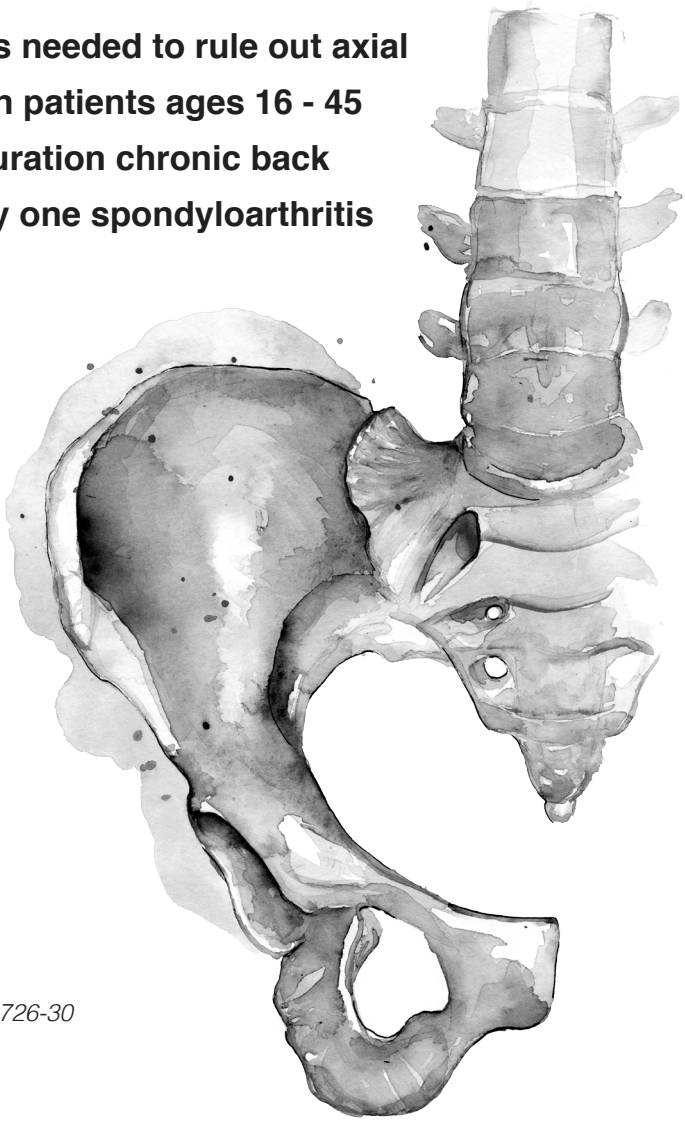

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ABSTRACT

Objective

To investigate whether HLA–B27 testing and imaging of the sacroiliac joints are needed in patients with ≤1 spondyloarthritis (SpA) feature, referred to a secondary care setting, after medical history collection, clinical examination, and measurement of acute phase reactants.

Methods

Baseline data from patients in the Spondyloarthritis Caught Early (SPACE) cohort visiting the rheumatology outpatient clinic of 5 centers across Europe (with back pain ≥3 months, ≤2 years, onset at ages <45 years) were used. All patients underwent a full diagnostic work-up: magnetic resonance imaging (MRI) and radiographs of the sacroiliac joints, HLA–B27 testing, and assessment of all other SpA features. Patients were diagnosed according to the treating rheumatologist and classified according to the Assessment of SpondyloArthritis international Society (ASAS) axial SpA criteria.

Results

Of the 354 patients, 133 (37.5%) showed 0 or 1 SpA feature after medical history collection, physical examination, and measurement of acute phase reactants (38 without SpA features, 95 with 1 SpA feature). Of the patients with ≤1 SpA feature, 18.4% (with 0 SpA features) and 17.9% (with 1 SpA feature) were diagnosed with axial SpA according to the rheumatologist after additional investigations (HLA–B27 testing and sacroiliac joint imaging). Additionally, 4 of 38 patients (10.5%) without SpA features fulfilled the ASAS axial SpA criteria (all according to the imaging arm only: 2 as MRI+/modified New York criteria (mNY)+,1 as MRI+/mNY-, and 1 as MRI-/mNY+). Of the 95 patients with 1 SpA feature, 22 (23.2%) fulfilled the ASAS axial SpA criteria (all according to the imaging arm only: 3 as MRI+/mNY+, 15 as MRI+/mNY-, and 4 as MRI-/mNY+).

Conclusions

In these patients in a secondary care setting with ≤1 SpA feature, axial SpA could not be ruled out without sacroiliac joint imaging and/or HLA–B27 testing.

INTRODUCTION

Axial spondyloarthritis (SpA) is a heterogeneous disease, and the diagnostic process can be challenging, since chronic back pain (CBP) is a very common symptom.[1] Nevertheless, diagnosis is important, as effective treatments are available and treatment at an early stage may lead to a better outcome, i.e., achieving low disease activity or even remission and possibly the prevention of structural damage as well.[2–6] Additionally, an early diagnosis reduces uncertainties in patients and prevents unnecessary diagnostic procedures.

In clinical practice, axial SpA can be diagnosed by recognition of a characteristic pattern of clinical, laboratory, and imaging findings. Through medical history collection, physical examination, and measurement of acute phase reactants, information on the presence of SpA features should be obtained in patients suspected of axial SpA (e.g., presence of enthesitis or uveitis anterior).[7] Additionally, testing for the presence of HLA–B27 and imaging of the sacroiliac (SI) joints using pelvic radiographs and/or magnetic resonance imaging may provide essential clues on the presence of axial SpA. The presence or absence of all those different SpA features determines the likelihood of diagnosis.[8] Unfortunately, there is no single SpA feature with sufficient specificity to establish the diagnosis early, and no formal diagnostic criteria exist.[9,10]

The modified Berlin algorithm may aid clinicians in establishing an early diagnosis of axial SpA with greater confidence.[11] According to the algorithm, an SI radiograph should be obtained in all patients with CBP (duration ≥3 months and ≤2 years, age at onset at ages <45 years) visiting the rheumatologist. Afterward, the presence of other SpA features should be evaluated. In case of 0 or 1 SpA feature, HLA–B27 testing is suggested, and if positive an MRI of the SI joints should be performed.

A downside of the algorithm is that radiographs are advised in all referred patients, regardless of the presence of other SpA features, meaning that all patients are subjected to ionizing radiation. Furthermore, after performing SI radiographs, medical history collection, physical examination, and measurement of acute phase reactants, the algorithm does not distinguish between patients with 0 or 1 SpA feature and recommends HLA–B27 testing in all patients, even though patients with no SpA features at that point may have a very low likelihood of axial SpA.

To address these issues, this study aimed to investigate whether additional investigations are useful in patients ages 16–45 years with back pain and ≤1 SpA feature (after clinical examination, physical examination, and C-reactive protein [CRP] level/erythrocyte sedimentation rate [ESR] measurement, but before HLA–B27 testing and imaging of the SI

joints). The study also aimed to investigate whether results are different in patients without SpA features or with 1 SpA feature.

METHODS

Study population

Baseline data from the Spondyloarthritis Caught Early (SPACE) cohort of patients included between January 2009 and October 2014 were used for this analysis. For this study, a subgroup of the SPACE cohort was used, namely patients with 0 or 1 SpA feature after medical history and physical examination, but before imaging and HLA–B27 testing. An extensive description of the cohort as a whole is available elsewhere.[12] In short, SPACE is a multinational, multicenter inception cohort study of young patients with CBP of a short duration (≥3 months but ≤2 years, with the onset at ages <45 years), with a suspicion of SpA referred to a rheumatologist.

Inclusion took place at 5 participating centers in The Netherlands (Leiden, Amsterdam, Gouda), Norway (Oslo), and Italy (Padua). Approval for the study was obtained from the local medical ethics committees. Patients were referred to the outpatient clinic of the different participating centers. All patients were first assessed by the rheumatologist. In case of suspected SpA, patients could be included in the SPACE cohort. Before inclusion, patients gave written informed consent in accordance with the declaration of Helsinki.

Diagnostic work-up

All patients underwent a full diagnostic work-up according to a fixed protocol. This work-up consisted of SI MRI and radiographs, HLA–B27 testing, and assessment of all other SpA features: inflammatory back pain (IBP), peripheral arthritis, enthesitis, acute anterior uveitis, dactylitis, psoriasis, inflammatory bowel disease (IBD), good response to nonsteroidal anti-inflammatory drugs (NSAIDs), a positive family history for SpA, and elevated CRP level and/or ESR.

Imaging of the SI joints

The MRIs were performed on a 1.5T machine. The acquired sequences were coronal oblique T1-weighted turbo spin-echo (repetition time [TR] 550/ echo time [TE] 10) and STIR (TR 2500/TE 60) with a slice thickness of 4 mm. The images were performed in a coronal oblique view. Radiologists of the different centers interpreted the radiographs and MRIs of the SI joints for the presence of sacroiliitis. This process was done as part of routine clinical practice, interpreting MRI using global assessment of the images (sacroiliitis yes/no) and interpreting radiographs according to the modified New York criteria. While reviewing the

images, radiologists took differential diagnoses such as hernia, osteoarthritis, and so on, into account.

Outcome: diagnosis of axial SpA and classification according to the Assessment of SpondyloArthritis international Society (ASAS) axial SpA criteria

Following the work-up discussed before (including HLA–B27 testing and imaging), the treating rheumatologist was asked to provide a diagnosis of axial SpA (yes/no) and provide a certainty of assessment for that diagnosis on a 1–10 scale. In addition, patients were classified according to the ASAS axial SpA criteria (yes/no).[13] This classification was done after all information, including imaging and HLA–B27 testing results, was obtained. Data were analyzed using Stata SE software, version 12.

RESULTS

In the SPACE cohort, after medical history collection, physical examination, and measurement of acute phase reactants, 133 of 355 patients (37.5%) had 0–1 SpA features, 44.7% had 2–3 SpA features, and 17.9% had ≥4 SpA features. For this study, the 133 patients with ≤1 SpA feature were included (95 with 1 SpA feature, 38 without SpA features). Patient characteristics for both groups are described in Table 1.

Table 1: Baseline characteristics of patients with ≤1 SpA feature

	Patients with 0 features Total number (n=38)	**Patients with 1 feature** Total number (n=95)	**All patients in the cohort** Total number n (n=354)
Age (years) at inclusion, mean (SD)	29.7 (9.6)	32.1 (8.4)	31.1 (8.4)
Male, n (%)	14 (36.8)	26 (27.4)	119 (33.6)
Symptom duration (months), mean (SD)	10.4 (6.1)	13.3 (7.5)	12.9 (7.2)
IBP, n (%)	-	38 (40.0)	220 (62.2)
Good response to NSAIDs, n (%)	-	12 (12.6)	119 (33.6)
Positive family history SpA, n (%)	-	20 (21.1)	130 (36.7)
Peripheral arthritis, n (%)	-	2 (2.1)	45 (12.7)
Dactylitis, n (%)	-	0 (0)	15 (4.2)
Enthesitis, n (%)	-	2 (2.1)	52 (14.7)
Uveitis, n (%)	-	1 (1.1)	26 (7.3)
IBD, n (%)	-	8 (8.4)	29 (8.2)
Psoriasis, n (%)	-	2 (2.1)	34 (9.6)
Elevated CRP, n (%)	-	8 (8.4)	76 (21.5)
HLA-B27 positive, n (%)	7 (18.4)	22 (23.2)	127 (35.9)
Sacroiliitis radiograph mNY, n (%)	3 (7.9)	7 (7.4)	36 (10.2)
Sacroiliitis MRI, n (%)	8 (21.1)	18 (19.0)	88 (24.9)

SpA, spondyloarthritis; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease; CRP, C-reactive protein; HLA-B27, human leukocyte antigen B27; mNY, modified New York criteria; MRI, magnetic resonance imaging.

Patients with 0 or with 1 SpA feature had a mean ± SD age of 29.7 ± 9.6 years and 32.1 ± 8.4 years, respectively. Mean duration of back pain was 10.4 ± 6.1 months and 13.3 ± 7.5 months, respectively. For comparison, disease characteristics of the SPACE cohort as a whole are shown in Table 1. In the group without SpA features, 18.4% was HLA-B27 positive versus 23.2% in the group with 1 SpA feature. Sacroiliitis on radiographs was seen in 7.9% and on MRI in 21.1% of patients without SpA features versus 7.4% and 19.0% (radiographs and MRI, respectively) of patients with 1 SpA feature (Table 1). Notable differences among the extra-articular manifestations in the group of patients with 1 SpA feature were seen: specifically, IBD (8.4%) was more frequently present, compared to uveitis (1.1%) and psoriasis (2.1%).

Of the 38 of 133 patients (28.6%) with no SpA features after additional investigations, 4 (10.5%) were classified according to the ASAS axial SpA criteria (Table 2). Three of those 4 were also diagnosed as having axial SpA by the rheumatologist. Four additional patients were diagnosed as having axial SpA by the rheumatologist but did not fulfill the ASAS axial SpA criteria.

A striking finding is that two of these patients were diagnosed as having axial SpA in the absence of both HLA–B27 positivity and sacroiliitis on both imaging modalities. In these two patients, certainty of diagnosis was 3 and 8, respectively (on a 1–10 scale, with 10 implying great certainty and 1 little certainty about diagnosis). Review of the MRI showed that the patient with a diagnosis of axial SpA with a high certainty (8 of 10) had clear evidence of SpA-associated structural lesions in the absence of inflammatory lesions on MRI or radiographic sacroiliitis. This evidence could have contributed to the SpA diagnosis.

Of the 95 of 133 patients (71.4%) with 1 SpA feature, 22 (23.2%) fulfilled the ASAS axial SpA criteria. Seventeen of the 95 patients (17.9%) were diagnosed as having axial SpA by the rheumatologist. Of these 17 patients, 14 were also classified via the ASAS axial SpA criteria, and the remaining 3 patients were not. In contrast, 5 patients were classified according to the ASAS axial SpA criteria, while not being diagnosed as having axial SpA according to the rheumatologist (data on diagnosis missing in 2 patients).

Of the patients with 1 feature who were classified according to the ASAS axial SpA criteria, the SpA features that were present before imaging and HLA–B27 testing were as follows: 7 patients had IBP, 5 had IBD, 4 had a positive family history for SpA, 3 had a good response to NSAIDs, 2 had elevated CRP levels and/or ESR, and 1 patient had enthesitis. The SpA features present in the patients who were diagnosed by a rheumatologist with axial SpA (among patients with 1 SpA feature) were as follows: 4 had a positive family history of SpA, 4 had IBP, 4 had IBD, 3 had an elevated CRP level and/or ESR, 1 had enthesitis, and 1 patient had a good response to NSAIDs.

In the 133 patients with ≤1 SpA feature, radiographic results were negative in 123 patients. Nineteen of those 123 patients (15%) were eventually diagnosed as having axial SpA after MRI and HLA–B27 testing were done. Of the 133 patients with ≤1 SpA feature, HLA–B27 was negative in 104 patients, of which 14 (13.5%) were eventually diagnosed with axial SpA. However, of the 133 patients, MRI was negative in 107, of which only 7 (6.5%) were diagnosed as having axial SpA.

Table 2: Effect of HLA–B27 testing and sacroiliac joint imaging on diagnosis and classification

Number of SpA-features	HLA-B27 status	Imaging status	SpA diagnosis yes	ASAS axSpA classification yes	SpA diagnosis no	ASAS axSpA classification no
0 (n=38)	HLA-B27 + (n=7)	MRI+ mNY+	2	2		
		MRI+ mNY-	1	1		
		MRI- mNY+		1	1	
		MRI- mNY-	2		1	3
	HLA-B27 – (n=31)	MRI+ mNY+				
		MRI+ mNY-	2		2*	5
		MRI- mNY+				
		MRI- mNY-			26	26
1 (n=95)	HLA-B27 + (n=22)	MRI+ mNY+		2	1*	
		MRI+ mNY-	3	4	1	
		MRI- mNY+		1	*	
		MRI- mNY-	2		12*	15
	HLA-B27 – (n=73)	MRI+ mNY+	1	1		
		MRI+ mNY-	8	11	3	
		MRI- mNY+	2	3	1	
		MRI- mNY-	1		57	58
Total			24	26	105	107

Asterisk (*) diagnosis by rheumatologist is missing.
SpA, spondyloarthritis; axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; ASAS, Assessment of SpondyloArthritis international Society; mNY, modified New York criteria; MRI, magnetic resonance imaging.

DISCUSSION

In patients with CBP referred to a rheumatologist and with ≤1 SpA feature, after full medical history collection, physical examination, and CRP level/ESR measurement, subsequent HLA–B27 testing and imaging led to a diagnosis of axial SpA in almost 20% of both patient groups. In both the group of patients with 0 SpA features and patients with 1 SpA feature, 20% were diagnosed with axial SpA, and therefore the number of SpA features present was not a differentiating factor in this study. Additionally, fulfilment of the ASAS axial SpA criteria was seen in 11% and 23% of the patients without SpA features and with 1 SpA feature, respectively.

Although we were expecting some patients to have a diagnosis of axial SpA, we were surprised by the relatively high percentages, in particular in the group with no SpA features. Several factors may have contributed to this unexpected finding. The preselection of patients could be an important explanation for this result: only patients ages <45 years were included and with a short duration of back pain (≤2 years). Diagnosis could also be influenced by the presence of SpA features that are not incorporated in the criteria, i.e., the presence of syndesmopohytes, inflammation on an MRI of the spine, or structural lesions on MRI of the SI joints. On the other hand, it is important to put the high percentages of an SpA diagnosis into perspective. Diagnosing SpA can be a challenge, especially in the absence of sacroiliitis on imaging. This clinical manifestation of SpA is heterogeneous, and diagnostic criteria are lacking.

A strength of this study is that we applied both diagnosis and classification. Taken together, these data support the ASAS modified Berlin algorithm in its recommendation to perform additional investigations in patients with 0 and 1 SpA feature in a secondary setting. Although differences exist between patients without and patients with 1 SpA feature, even in patients without SpA features, after medical history collection, physical examination, and CRP level/ESR measurement, we cannot entirely rule out axial SpA.

However, it should be taken into account that the SPACE cohort consists of patients with CBP with ≤2 years of symptoms. As radiographic changes may develop over time[14] radiography may not be the ideal first diagnostic step (as the modified Berlin algorithm suggests) in these young patients with a short symptom duration. This conclusion was underlined by the fact that the yield of radiographs was very low in this study, and as a comparison the yield of MRI is much higher. For future studies, investigating the additional benefit of structural lesions on a T1-weighted MRI of the SI joints should be relevant.

A limitation of this study is that the radiologists performed a global assessment of sacroiliitis rather than the ASAS definition for a positive MRI, and that we used this global assessment while applying the ASAS axial SpA classification criteria.[15] In addition, and in line with common clinical practice, only one reader interpreted the images instead of reading by several readers, although we assume that in the majority of cases the treating rheumatologist read the images as well.

An important strength of the study is that SPACE is an inception cohort for young patients with CBP (duration ≥3 months and ≤2 years, onset at ages <45 years), allowing us to investigate whether patients with very few symptoms can still be diagnosed and classified as having axial SpA. To our knowledge, SPACE is currently one of the very few, if not the only, sufficiently large longitudinal cohort study in the field of spondyloarthritis where patients without SpA features can also be included, which has allowed us to perform the current study. Since this study was performed in a secondary-care setting (patients referred to a rheumatologist, with a suspicion for axial SpA), we would like to emphasize that the results of this study cannot be extrapolated to CBP patients where the prevalence of axial SpA is much lower, as in primary care.

In conclusion, in a secondary-care setting, in patients with ≤1 SpA feature, after full medical history collection, physical examination, and CRP level/ESR measurement, axial SpA cannot be ruled out without additional imaging and/or HLA–B27 testing. In addition, these results also show that in selected cases diagnosis is entirely based on HLA–B27 testing and imaging.

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Assessment of sacroiliitis by radiographs and MRI: where are we now?

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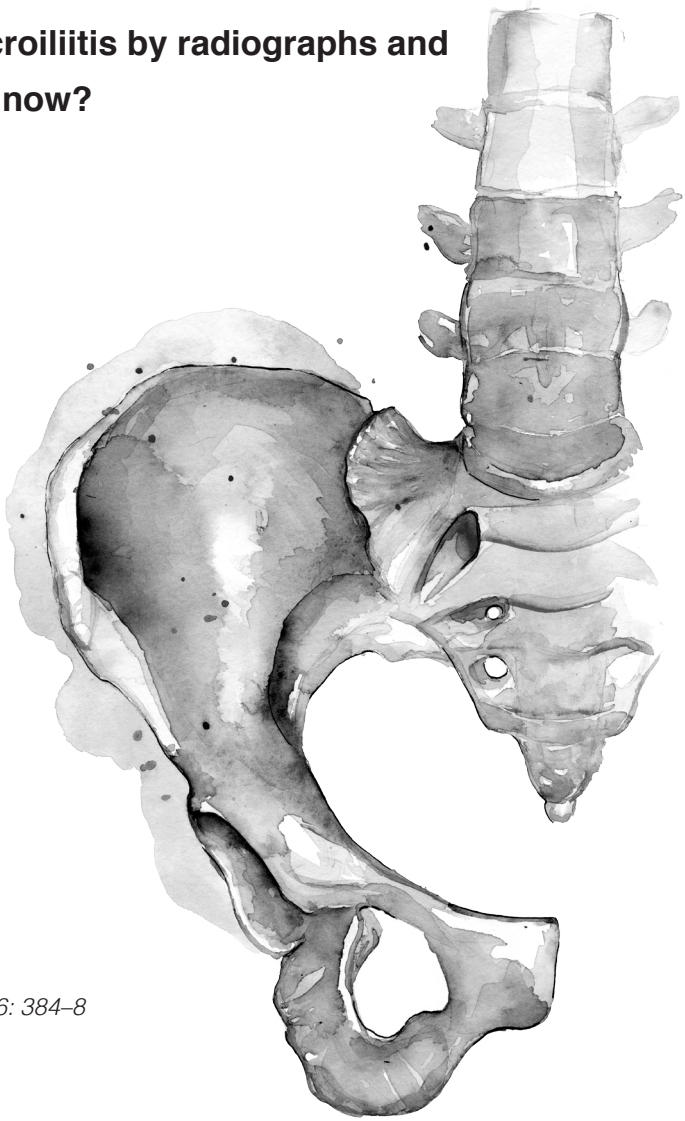

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ABSTRACT

Purpose of review

Both MRI and plain radiography are used to assess sacroiliitis. A weakness of radiography, apart from its inability to detect early disease, is reader variability. On the contrary, experience with MRI is relatively limited by comparison.

Recent findings

This review summarizes recent advances in sacroiliac joint imaging using radiography and MRI in spondyloarthritis.

Summary

Observer variation in reading radiographs of sacroiliac joints remains an unresolved issue. In recent years, more studies on MRI in the diagnosis of axial spondyloarthritis have become available. Incorporating structural lesions in the sacroiliac joint and spine and inflammatory lesions in the spine in the definition of a positive MRI are hot topics in research.

Keypoints

- Reader variability in reading radiographs of the sacroiliitis joints remains unresolved.
- As a result, there is concern about the reliability of radiographs of the sacroiliac joints in diagnosing axial SpA.
- Although more data are becoming available, the number of high-quality studies on the diagnostic utility of MRI of the sacroiliac joints is relatively limited.
- Incorporation of structural changes into the definition of a positive sacroiliac MRI is an important line of current research.

INTRODUCTION

Sacroiliitis is the hallmark of axial spondyloarthritis (SpA).[1] Axial SpA is called non-radiographic axial SpA when there are no (definite) abnormalities detected on plain film radiographs of the sacroiliac joint and is called radiographic axial SpA or ankylosing spondylitis (AS) when definite signs of sacroiliitis are seen on radiographs of the sacroiliac joints.[2]

Radiography is the method most commonly used to assess involvement of the sacroiliac joint, but it is often inadequate to detect early disease, as patients may have symptoms for several years before abnormalities can be seen on radiography.[3] Moreover, reading radiographs of the sacroiliac joints are considered difficult. Interobserver and intraobserver variations are substantial, which implies that sacroiliitis is often missed or incorrectly diagnosed.[4]

van Tubergen et al. set out to investigate if training could improve performance of radiologists and rheumatologists in reading radiographs of the sacroiliac joints.[4] One hundred rheumatologists and 23 radiologists took part in the study wherein sensitivity was assessed using sacroiliac joint radiographs of Human Leukocyte Antigen (HLA)-B27-positive AS patients, and specificity was assessed using radiographs of healthy HLA-B27-negative relatives. Participants scored radiographs at baseline, 3 months later after following a self-education program and again 3 months later after attending a workshop.

At baseline, median sensitivity of rheumatologists for detecting sacroiliitis on radiographs was 81% (range 31–100%) with a specificity of 75% (range 38–100%). After self-education, median sensitivity dropped to 75% (range 25–100%), whereas specificity increased to 78% (range 44–100%). After the workshop, the sensitivity then returned to 81% (range 25–100%), and specificity was stable at 79% (range 39–96%). The results of the radiologists showed similar fluctuations. At baseline, median sensitivity of radiologists for detecting sacroiliitis on radiographs was 88% (range 25–100%) with a specificity of 71% (range 46–100%). After self-education, median sensitivity dropped to 78% (range 44–100%), whereas specificity was 73% (range 38–96%). After the workshop, the sensitivity and specificity then increased to 84% (range 50–100%) and 85% (range 50–96%), respectively.

Intraobserver variation was tested using a set of 10 radiographs with various degrees of sacroiliitis. Agreement was high for radiographs without signs of sacroiliitis or complete ankylosis of sacroiliac joints (range of means 94–100%), but much lower for radiographs with more subtle changes (grade 1 or 2 sacroiliitis) with mean agreements ranging from 52 to 87%.

This study is important for several reasons. First, it shows that rheumatologists and radiologists have only modest sensitivity and specificity for diagnosing sacroiliitis using radiographs alone. In addition, there is considerable intraobserver variability particularly when changes

because of sacroiliitis are subtle. Most importantly, however, this study shows that training of readers of radiographs does not improve their sensitivity or specificity. This means that, in its current form, there is concern about the reliability of conventional radiographs of sacroiliac joints when used for diagnosis.

MRI has proven capable of detecting inflammatory lesion in the sacroiliac joints in SpA before changes are seen on radiographs. An indication of the increased use of MRI in SpA is the inclusion of MRI of the sacroiliac joints in the Assessment of SpondyloArthritis international Society (ASAS) axial SpA classification criteria.[5] MRI of the sacroiliac joints is able to detect several features associated with sacroiliitis, such as ankylosis, bone marrow edema (BME)/ osteitis, capsulitis, enthesitis, erosions, fat deposition and synovitis. However, a 2009 report by radiologists and rheumatologists from the ASAS/ Outcome Measures in Rheumatology (OMERACT) MRI working group considered clear presence of BME essential for defining active sacroiliitis. In what has become known as the ASAS definition for a positive MRI, a BME lesion highly suggestive of sacroiliitis needs to be present in subchondral or periarticular bone. If there is only one signal (BME lesion) on an MRI slice, this BME lesion should be present on at least two consecutive slices, although when there are two or more BME lesions on a single slice, one slice is sufficient.[6]

A systematic review published in 2012 reviewed the literature on MRI in SpA published until November 2011. The aim of the review was to determine the level of evidence for the utility of MRI in relation to the clinical diagnosis of SpA.[7] Studies included in the review had to be case–control or cohort studies and had to include the arbitrary number of more than 20 patients and 20 controls. After literature search, 76 full text articles were reviewed with only nine studies included in the review. Of these nine studies, only two met the authors' criteria for a high-quality report. Of these two reports, one reported on MRI abnormalities in the spine and one on MRI abnormalities in the sacroiliac joints. The authors of the review concluded that because of the small number of high-quality studies, current evidence for MRI in the diagnosis of axial SpA is limited.

With data showing that education does not improve reading radiographs of the sacroiliac joints and a review concluding that there are not enough studies demonstrating the diagnostic utility of MRI for sacroiliitis, we searched the literature for recent studies to see what progress has been made in recent years on the two most commonly used imaging modalities for detecting sacroiliitis.

LITERATURE SEARCH

PubMed, Embase, Web of Science and the Cochrane Library were searched in November of 2013 for articles on interobserver and intraobserver variability of radiographs of the sacroiliac joints in SpA and on the diagnostic value of MRI of the sacroiliac joints in SpA using two separate search strategies. The search strategy used for PubMed can be found in Supplementary Table 1. All articles were reviewed by title and abstract by two out of three assessors (F.G., P.B. and M.H.), and an article was selected if both assessors agreed that the study contained data relevant to the search. The literature search for articles on radiographs was limited to publications after the study by Van Tubergen et al. was published in 2003, and the search for MRI was limited to publication from 2010 onward, as the review by Arnbak et al. had covered all articles published before 2011.[4,7]

RECENT LITERATURE ON OBSERVER VARIATION IN READING RADIOGRAPHS OF THE SACROILIAC JOINTS

With the search strategy for radiographs, 800 articles were found in the databases. After review, five full text articles and one meeting abstract were identified as containing relevant data.

In their 2004 study, Spoorenberg et al. compared reliability and change over time of several radiological scoring methods in AS, including grading of sacroiliac joints using the 0–4 New York method and the almost identical Stoke Ankylosing Spondylitis Spine Score.[8] Radiographs of 217 AS patients at baseline, 12 and 24 months were scored by two observers. Kappa values for intraobserver variability ranged from 0.36 to 0.76 and interobserver variability ranged from 0.66 to 0.70. Kappa coefficients are a statistical measure of interreader agreement that are thought to be more robust than simple agreement calculation as kappa takes agreement occurring by chance into account. Using the cutoff values proposed by Landis and Koch, in this study, the kappa for intraobserver variability indicates fair to substantial agreement and moderate-to-substantial agreement for interobserver variability.[9] In the same year, another study on radiological scoring methods for AS by the same group was published, but this did not provide separate results on variability of scoring sacroiliac joints radiographs.[10]

An example of how variability in grading sacroiliac radiographs may affect clinical practice is provided by data from the multicenter German Spondyloarthritis Inception cohort (GESPIC) cohort.[11] Radiographs of the sacroiliac joints of 149 non-radiographic SpA and 182 AS patients were rescored by two central readers. After rescoring, 11.4% AS patients were reclassified into non-radiographic axial SpA, and 15.5% non-radiographic axial SpA were reclassified into

AS. Agreement between the two readers was modest [intraclass correlation coefficient (ICC)] for the left sacroiliac joint, 0.36 [95% confidence interval (CI) 0.22–0.49] and for the right sacroiliac joint, ICC 0.36 (95% CI 0.22–0.49). In a more recent study from the GESPIC cohort kappa values for scoring the sacroiliac joints ranged from 0.51 to 0.59 between two readers indicating moderate agreement.[12]

In a study assessing the performance of computed tomography (CT) of the sacroiliac joints in patients with suspected SpA, two radiologists independently read 100 paired radiographs and CT scans. Similarly to previous studies, interreader variability was moderate for sacroiliitis on radiographs (kappa 0.59) but was much better for CT scans of the sacroiliac joints (interobserver kappa 0.91).[13]

In summary, all studies published in the past 10 years confirm the substantial interobserver and intraobserver variability in grading radiographs of the sacroiliac joints for sacroiliitis, but we found no progress in solving or reducing the problem by education or technical innovation. A possible exception was a meeting abstract reporting slightly better performance of posterior-anterior projection as compared with anterior-posterior projection in radiographs of the sacroiliac joints, but the data have not yet been published.[14]

RECENT LITERATURE ON THE DIAGNOSTIC UTILITY OF MRI FOR SACROILIITIS IN SPONDYLOARTHRITIS

With the search strategy for MRI, 1094 articles and meeting abstracts published since 2010 were found in the databases. After review, four full text articles were identified as containing relevant data.

Because of several months' overlap of the literature search, the first article found was the one high-quality study described in the aforementioned systematic review.[7] Weber et al. published data from a cross-sectional, international multicenter study called MORPHO.[15] Aim of the study was to assess the diagnostic utility of MRI in SpA and construct a definition for a positive MRI. After calibrating readers using a training set, five readers independently read MRI scans from 75 patients with AS, 27 patients with inflammatory back pain (IBP) suspected of having SpA, 26 patients with nonspecific back pain and 59 healthy controls. AS was diagnosed according to the modified New York criteria, IBP was defined by expert opinion, the Calin IBP criteria or the Berlin IBP criteria, and nonspecific back pain was defined on clinical grounds. For all MRIs, BME, erosions, fat infiltration and ankylosis were scored by the readers, and readers were asked if they thought the MRI scan confirmed the presence of SpA by global assessment. Using global assessment of the MRI, agreement for the diagnosis of SpA in

IBP patients was 85% for all five readers and agreement for the absence of SpA was 92% in nonspecific back pain patients and 95% in healthy controls.

Comparing IBP patients with patients with non-specific back pain and controls, the global assessment of the readers had a sensitivity of 51% and a specificity of 98%. The ASAS definition of a positive MRI using BME only had a sensitivity of 67% and a specificity of 88% and a new proposed definition based on BME and erosions (MORPHO definition) had a sensitivity of 81% and a specificity of 88%. Comparing AS patients with nonspecific back pain patients and controls, global assessment had a sensitivity of 90% and a specificity of 97%, and the ASAS definition had a sensitivity of 85% and a specificity of 88%.

In a study from the same group, the same number of MRIs was scored by a different number of readers, and this study showed that besides BME structural lesions, such as erosions, are commonly seen in AS and IBP although erosions were now more often scored in nonspecific back pain patients and controls than in their previous study.[16] The authors subsequently published a study using selected patients and controls from the previous two studies.[17] MRIs of the sacroiliac joints of 30 AS patients and 30 controls were used to assess the reproducibility of scoring erosions using four readers. The kappa value for scoring erosions was 0.72, which was slightly higher than the kappa of 0.61 for scoring BME.

In their next article, Weber et al. took a slightly different approach by using both the consensus classification of an MRI as SpA or no-SpA using global assessment and the clinical diagnosis as the gold standard for disease.[18] In the consensus classification, an MRI was marked as consistent with SpA when at least three out of four readers thought the images showed signs of SpA. An MRI was marked as no-SpA when all readers thought that the images showed no signs of SpA with a high confidence.

MRIs of the sacroiliac joints from two inception cohorts were scored for presence of BME, erosions and fat infiltration by all four readers using a scoring system wherein the sacroiliac joint is represented by four quadrants (upper ilium, lower ilium, upper sacrum and lower sacrum). Cohort A consisted of 10 healthy controls and 79 patients of which 10 had AS, 20 non-radiographic axial SpA and 39 nonspecific back pain. Cohort B consisted of 88 patients with an acute uveitis and back pain who were referred to a rheumatologist. Diagnosis was made based on the clinical opinion of a rheumatologist. In this cohort, 31 patients had non-radiographic axial SpA, 24 AS and 33 patients with nonspecific back pain.

Using the consensus classification of sacroiliac joint MRI as the gold standard, to reach a preset specificity of 90%, BME had to be present in two sacroiliac joint quadrants. At this cutoff which the authors state is similar to the ASAS definition, sensitivity was 91% in cohort A and 83% in cohort B. To reach 90% specificity, only one erosion had to be present in both

cohorts giving a perfect sensitivity of 100%. Using the clinical diagnosis as the standard, BME had to be present in three sacroiliac quadrants in cohort A and in four sacroiliac quadrants in cohort B to reach a specificity of 90%. At this cutoff, sensitivities were 73% for cohort A and 39% for cohort B. To reach 90% specificity, one erosion had to be present in cohort A and two erosions in cohort B, and this had a sensitivity of 77 and 54%, respectively. The combined features of BME and/or erosion had a sensitivity of 82% for cohort A and 51% for cohort B with a specificity of 90%. Irrespective of the standard used, fat infiltration performed worse than BME and erosions. The authors conclude that these results support the use of both BME and erosions in defining a positive MRI sacroiliac in axial SpA.

DISCUSSION

The literature of the past 10 years confirmed reader variability in reading radiographs of the sacroiliac joints, but no progress was made in reducing the variability. As the example of reclassification of AS and non-radiographic axial SpA patients by central readers in the GESPIC cohort exemplifies, physicians should be careful in making or rejecting the diagnosis of axial SpA based on radiographs of the sacroiliac joints alone.

Given the curved shape of the sacroiliac joint, which complicates radiography, CT has been investigated as an alternative imaging modality in suspected SpA and AS.[13,19] However, a disadvantage of CT scans is that the radiation dose is higher than for radiographs. Given that axial SpA usually start in young adults: this is particularly an issue for young women in whom the ovaries are within the primary CT beam. Low radiation CT scanning protocols of the sacroiliac joints have been developed but are not in widespread use.[20]

The literature on MRI of the sacroiliac joints in SpA of the last 3 years consisted of publications from a consortium from Switzerland, Denmark and Canada. One thing that is clearly encouraging about their data is that they showed that their expert readers had a good agreement on diagnosing SpA or no-SpA using MRI. In addition, another group reported substantial or almost perfect interreader variability in scoring MRI sacroiliac changes.[21] So, the available data indicate that MRI of the sacroiliac joints has an acceptable interreader variability.

Weber and colleagues advocate the incorporation of structural changes into the definition of a positive sacroiliac MRI for SpA, as this could improve sensitivity and specificity. However, more studies are needed, and a generally accepted definition of what constitutes structural changes consistent with SpA has yet to be decided.

Another possibility to improve the diagnostic utility of MRI scanning is to look for inflammatory or structural lesions in the spine. A consensus-based definition of a positive spinal MRI for inflammatory lesions (spondylitis) and structural changes (fat deposition) has been published, and spinal inflammation detected in the absence of inflammation in the sacroiliac joints has been observed in SpA patients, but more studies are needed.[22,23]

The number of high-quality studies on the diagnostic utility of MRI of the sacroiliac joints remains relatively limited. However, following the publication of the ASAS axial SpA classification criteria, interest in the early stage of axial SpA has increased greatly in recent years. Therefore, it is to be expected that the number of studies on MRI imaging in axial SpA from cross-sectional studies, clinical trials and inception cohorts will increase in the coming years.

CONCLUSION

In axial SpA, no progress has been made in radiography of the sacroiliac joints in recent years, but there is steady progress in research on diagnostic utility and reliability of MRI of the sacroiliac joints.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Search strategy used in the Pubmed database for observer variability in reading radiographs of the sacroiliac joint (A) and the diagnostic utility of magnetic resonance imaging for sacroiliitis (B). All articles in the article were found using these strategies.

A: Observer variability in reading radiographs of the sacroiliac joint

((("Sacroiliac Joint"[Mesh] OR "sacroiliac"[all fields] OR "sacro-iliac"[all fields] OR "Sacroiliitis"[Mesh] OR "Sacroiliitis"[all fields] OR sacroili*[all fields]) **AND** ("X-Rays"[majr] OR "Radiography"[majr:noexp] OR "Radiographic Image Enhancement"[majr] OR "Radiographic Image Interpretation, Computer-Assisted"[majr] OR "Radiographic Magnification"[majr] OR "Radiography, Interventional"[majr] OR "Tomography, X-Ray "[majr] OR "Xeroradiography"[majr] OR "x rays"[ti] OR "x ray"[ti] OR "x-rays"[ti] OR "x-ray"[ti] OR "xrays"[ti] OR "xray"[ti] OR "x rayed"[ti] OR "x-rayed"[ti] OR "xrayed"[ti] OR "roentgen"[ti] OR "rontgen"[ti] OR "röntgen"[ti] OR roentgen*[ti] OR rontgen*[ti] OR röntgen*[ti] OR radiograph*[ti]) AND ("Spondylarthritis"[mesh] OR "spondyloarthritis"[all fields] OR "Spondylarthritides"[all fields] OR "Spinal Arthritis"[all fields] OR "Spondylitis, Ankylosing"[mesh] OR "ankylosing spondylitis"[all fields] OR "Bechterew Disease"[all fields] OR "Bechterew's Disease"[all fields] OR "Bechterews Disease"[all fields] OR "Ankylosing Spondyloarthritis"[all fields] OR "Rheumatoid Spondylitis"[all fields] OR "Spondylarthritis Ankylopoietica"[all fields] OR "Ankylosing Spondylarthritis"[all fields] OR "Ankylosing Spondylarthritides"[all fields] OR "Ankylosing Spondylitis"[all fields] OR "Marie-Struempell Disease"[all fields] OR "Marie Struempell Disease"[all fields] OR "Spondylarthropathies"[all fields] OR "Spondyloarthropathies"[all fields] OR "Marie-Strumpell Spondylitis"[all fields] OR "Marie Strumpell Spondylitis"[all fields] OR "Spondyloarthropathy"[all fields] OR "Spondyloarthropathies"[all fields] OR "Spondylarthropathy"[all fields] OR "Spondyloarthropathy"[all fields] OR "Sacroiliitis"[mesh] OR "sacroiliitis"[all fields] OR "Arthritis, Psoriatic"[mesh] OR "psoriasis arthritis"[all fields] OR "psoriatic arthritis"[all fields] OR "Psoriasis Arthropathica"[all fields] OR "Arthritic Psoriasis"[all fields] OR "Arthritis, Reactive"[mesh] OR "Reactive Arthritides"[all fields] OR "Reactive Arthritis"[all fields] OR "Post-Infectious Arthritis"[all fields] OR "Post Infectious Arthritis"[all fields] OR "Postinfectious Arthritis"[all fields] OR "Postinfectious Arthritides"[all fields] OR "Reiter Syndrome"[all fields] OR "Reiter's Disease"[all fields] OR "Reiters Disease"[all fields] OR "Reiter Disease"[all fields] OR "inflammatory back pain"[all fields] OR (("Arthritis"[mesh] OR "arthritis"[all fields]) AND ("Inflammatory Bowel Diseases"[mesh] OR "inflammatory bowel disease"[all fields] OR "inflammatory bowel diseases"[all fields] OR "ibd"[all fields] OR "crohn disease"[all fields] OR "crohns disease"[all fields] OR "crohn's disease"[all fields] OR "Ulcerative Colitis"[all fields])))**)** AND ("2002/01/01"[PDAT] : "3000/12/31"[PDAT])**) OR (**("Sacroiliac Joint"[Mesh] OR

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B: The diagnostic utility of magnetic resonance imaging for sacroiliitis

("Magnetic Resonance Imaging"[Mesh] OR "magnetic resonance imaging"[all fields] OR "NMR Imaging"[all fields] OR "MR Tomography"[all fields] OR "MR Imaging"[all fields] OR "MRI Imaging"[all fields] OR "NMR Tomography"[all fields] OR "Proton Spin Tomography"[all fields] OR "Magnetization Transfer Contrast Imaging"[all fields] OR "MRI Scans"[all fields] OR "MRI Scan"[all fields] OR "fMRI"[all fields] OR "Functional MRI"[all fields] OR "Functional MRIs"[all fields] OR "Chemical Shift Imaging"[all fields] OR "MRI"[all fields]) AND ("Spondylarthritis"[Mesh] OR "spondyloarthritis"[all fields] OR "Spondylarthritides"[all fields] OR "Spinal Arthritis"[all fields] OR "Spondylitis, Ankylosing"[Mesh] OR "ankylosing spondylitis"[all fields] OR "Bechterew Disease"[all fields] OR "Bechterew's Disease"[all fields] OR "Bechterews Disease"[all fields] OR "Ankylosing Spondyloarthritis"[all fields] OR "Rheumatoid Spondylitis"[all fields] OR "Spondylarthritis Ankylopoietica"[all fields] OR "Ankylosing Spondylarthritis"[all fields] OR "Ankylosing Spondylarthritides"[all fields] OR "Ankylosing Spondylitis"[all fields] OR "Marie-Struempell Disease"[all fields] OR "Marie Struempell Disease"[all fields] OR "Spondylarthropathies"[all fields] OR "Marie-Strumpell Spondylitis"[all fields] OR "Marie Strumpell Spondylitis"[all fields] OR "Spondyloarthropathy"[all fields] OR "Spondyloarthropathies"[all fields] OR "Spondylarthropathy"[all fields] OR "Sacroiliitis"[Mesh] OR "sacroiliitis"[all fields] OR "Arthritis, Psoriatic"[Mesh] OR "psoriasis arthritis"[all fields] OR "psoriatic arthritis"[all fields] OR "Psoriasis Arthropathica"[all fields] OR "Arthritic Psoriasis"[all fields] OR "Arthritis, Reactive"[Mesh] OR "Reactive Arthritides"[all fields] OR "Reactive Arthritis"[all fields] OR "Post-Infectious Arthritis"[all fields] OR "Post Infectious Arthritis"[all fields] OR "Postinfectious Arthritis"[all fields] OR "Postinfectious Arthritides"[all fields] OR "Reiter Syndrome"[all fields] OR "Reiter's Disease"[all fields] OR "Reiters Disease"[all fields] OR "Reiter Disease"[all fields] OR inflammatory back pain OR (("Arthritis"[mesh] OR "arthritis"[all fields]) AND ("Inflammatory Bowel Diseases"[Mesh] OR "inflammatory bowel disease"[all fields] OR "inflammatory bowel diseases"[all fields] OR "ibd"[all fields] OR "crohn disease"[all fields] OR "crohns disease"[all fields] OR "crohn's disease"[all fields] OR "Ulcerative Colitis"[all fields])))

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5

Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group

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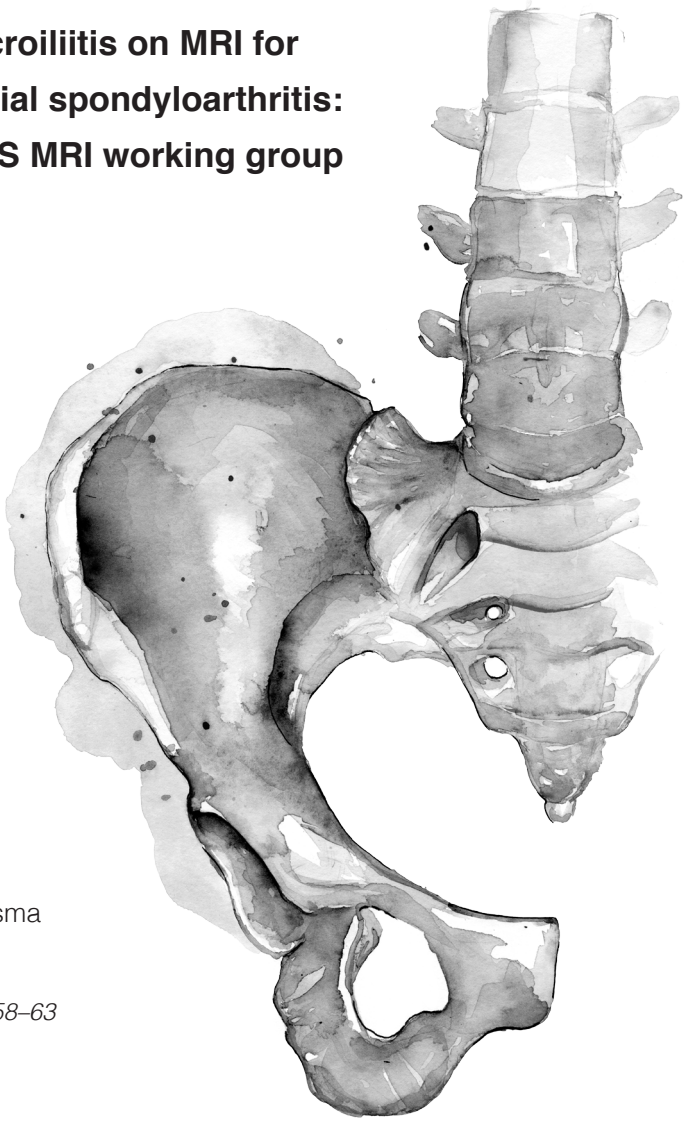
Ann Rheum Dis 2016;75: 1958–63



ABSTRACT

Objective

To review and update the existing definition of a positive MRI for classification of axial spondyloarthritis (SpA).

Methods

The Assessment in SpondyloArthritis International Society (ASAS) MRI working group conducted a consensus exercise to review the definition of a positive MRI for inclusion in the ASAS classification criteria of axial SpA. Existing definitions and new data relevant to the MRI diagnosis and classification of sacroiliitis and spondylitis in axial SpA, published since the ASAS definition first appeared in print in 2009, were reviewed and discussed. The precise wording of the existing definition was examined in detail and the data and a draft proposal were presented to and voted on by the ASAS membership.

Results

The clear presence of bone marrow oedema on MRI in subchondral bone is still considered to be the defining observation that determines the presence of active sacroiliitis. Structural damage lesions seen on MRI may contribute to a decision by the observer that inflammatory lesions are genuinely due to SpA but are not required to meet the definition. The existing definition was clarified adding guidelines and images to assist in the application of the definition.

Conclusions

The definition of a positive MRI for classification of axial SpA should continue to primarily depend on the imaging features of 'active sacroiliitis' until more data are available regarding MRI features of structural damage in the sacroiliac joint and MRI features in the spine and their utility when used for classification purposes.

INTRODUCTION

Since the early 1990s MRI has been increasingly used to visualise inflammation in the sacroiliac (SI) joints and spine and it has become clear that inflammatory lesions can be visible on MRI before structural changes are detectable on radiography or CT.[1] In 2009, the Assessment in SpondyloArthritis International Society (ASAS) published new criteria for axial spondyloarthritis (SpA) based on principles that incorporated demographic, clinical, laboratory and imaging components but now added an MRI definition so as to enable the identification of patients without evidence of structural change on radiography.[2] A 'positive MRI' was defined in a publication which described and illustrated the variety of lesions that may be encountered on MRI of SI joints showing sacroiliitis and its differential diagnoses, and also defined the nature and extent of inflammation in the SI joints that would be necessary to meet the definition of 'MRI positive for active sacroiliitis'.[3] The definition relied on the observation of inflammation seen in subchondral bone and other observations were not required as part of the MRI definition.

As only 30%–50% of subjects with axial SpA are positive for active sacroiliitis on MRI[4-6] the question arose as to whether the wording of the current definition for a positive MRI is appropriate and whether structural change of the SI joint or findings on spine MRI should be incorporated into the ASAS definition of a positive MRI. The purpose of this consensus exercise was to examine and discuss whether data published in the last 5 years relevant to the diagnosis and classification of axial SpA are sufficient to merit a change in the MRI definition of a positive MRI and clarify any misunderstanding of the existing definition that may have become apparent since its first publication.

METHODS

This manuscript has been developed on the basis of participation by 16 rheumatologists and 4 radiologists and 1 research fellow of the ASAS MRI working group with interest and experience in both SpA and MRI in a consensus exercise; presentation and discussion of evidence at a meeting on 5 September 2013 in Dusseldorf, Germany by the ASAS MRI working group; after refining the scope of the review, presentation during the annual assembly of ASAS on 17 January 2014 with voting on proposals open to all members; and consensus approval of the final manuscript by the members of the ASAS MRI working group.

Through the above process, the group was tasked with answering four questions related to MRI for inclusion in the ASAS classification criteria of axial SpA: (A) How does the current ASAS definition for a positive MRI perform? (B) Do we need to update the existing definition?

(C) Do we need to add MRI features of structural changes of the SI joint to the definition? (D) Do we need to include features of SpA on MRI of the spine in the definition? At the consensus meeting, an updated systematic literature review was presented, followed by review of the definition of a positive MRI scan of the SI joint and the definition of a positive MRI scan of the spine. Next, new data (partly unpublished at that time but published and cited since) related to one or more of the study questions were presented by members of the group. Finally, the precise wording of the existing definition was examined in detail. During the 2014 annual assembly of ASAS a summary of the data and the draft proposal of the group was presented followed by voting open to all full ASAS members.

RESULTS

There was consensus that there was no need to change the existing technical requirements necessary to reliably detect MRI features of inflammation or structural damage in bone marrow. As the presence of inflammation is the principal observation required by the current definition, this must be a focus for the MRI scan. The terms 'bone marrow oedema' (BMO) and 'osteitis' are considered to be equivalent in this context and the inflammatory and structural lesions have been previously described. The description for SI joint BMO is:

- BMO is depicted as a hyperintense signal on short tau inversion recovery (STIR) images (or equivalent water-sensitive sequences) and usually as a hypointense signal on T1-weighted images (Figure 1). The more intense the signal the more likely that it reflects active inflammation. A strong hyperintense signal is similar to that of cerebrospinal fluid. The sacral interforaminal bone marrow signal forms the reference for assignment of normal signal in the bone.
- BMO is an indicator of active sacroiliitis but may be found in other diseases (Figure 2) or as an incidental finding (Figures 3 and 4).
- Affected bone marrow areas are typically located periarticularly (subchondral bone marrow).
- BMO may be associated with signs of structural damage such as sclerosis or erosion (Figure 5).

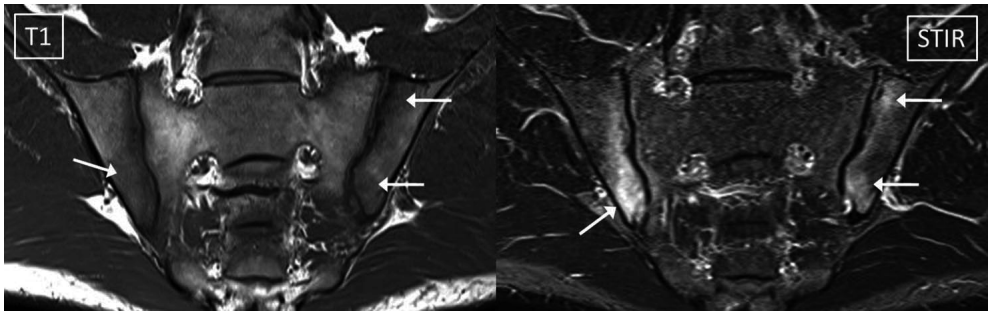


Figure 1: MRI sacroiliac (SI) joints—typical inflammatory sacroiliitis in non-radiographic axial spondyloarthritis. MRI of SI joints in a 26-year-old male with inflammatory low back pain of more than 3 months duration. C-reactive protein was 49.3 mg/L and HLA-B27 was positive. Pelvic radiograph was suspicious for spondyloarthritis but did not meet the definition for a positive radiograph according to the modified New York criteria—right SI joint grade 1 and left SI joint grade 0. The short tau inversion recovery (STIR) sequence shows abnormal increased signal (arrows) in the iliac bones bilaterally, typical for bone marrow oedema (BMO) due to inflammatory sacroiliitis. All the BMO are subchondral in location; the BMO is multifocal; each lesion is of a significant size; their margins are poorly defined; the right lower iliac lesion is larger and part of this lesion is intensely bright, similar in signal intensity to cerebrospinal fluid (not shown); and there are corresponding areas of diminished signal intensity on the T1-weighted sequence (arrows on T1). No erosion or other evidence of structural damage was visible on MRI or radiography. All these features are typical for inflammatory sacroiliitis.

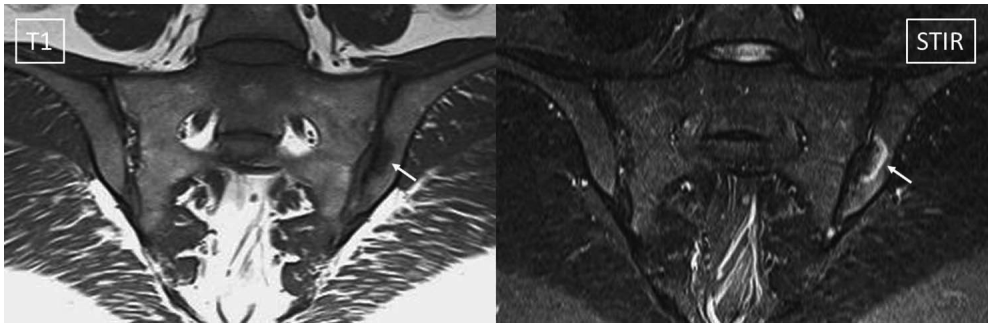


Figure 2: MRI sacroiliac (SI) joints—Osteitis Condensans Ilii (OCI). MRI of SI joints in a 28-year-old female with persistent low back and buttock pain of 4 years duration was performed 1 year after the second pregnancy. C-reactive protein was normal and HLA-B27 was positive. Pelvic radiograph revealed bilateral iliac sclerosis with joint space narrowing and minimal irregularity of the joint surface. The short tau inversion recovery (STIR) sequence shows abnormal increased signal (arrow) in the left iliac bone, with a non-specific appearance. The BMO has an arcuate contour surrounding an area of diminished signal intensity on the T1-weighted sequence (arrow on T1) that corresponded to radiographic sclerosis. More prominent sclerosis and less intense BMO were seen on multiple slices. The subchondral location of the finding may be seen in lesions related to either spondyloarthritis or mechanical causes. The very sharp definition of the borders of the abnormality does not help distinguish the etiology. The T1 sequence did not show evidence of structural damage (erosion, fat metaplasia or ankylosis) except for sclerosis, which is a non-specific observation. The patient was followed up for 10 years and a diagnosis of OCI was subsequently confirmed.

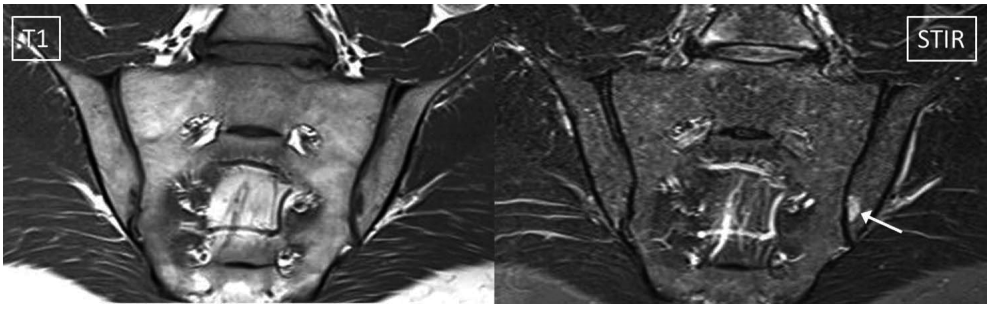


Figure 3: MRI sacroiliac (SI) joints—mechanical back pain. MRI of SI joints in a 31-year-old male with mechanical low back pain of more than 3 months duration. C-reactive protein was normal. On pelvic radiography, the SI joints were normal. The short tau inversion recovery (STIR) sequence shows abnormal increased signal (arrow) in the subchondral bone of the left ilium with a non-specific appearance. Although a BMO lesion is clearly present, it is small and on the T1-weighted sequence an even smaller focus of very low signal is seen in the same location paralleling the articular surface. There was no evidence of structural damage in the SI joints. These coronal images also show evidence of disc degeneration at L5/S1 with loss of height and signal intensity of the nucleus pulposis, bulging annulus and Modic type 1 reactive inflammation (bright on STIR) at the perimeter of the disc. The patient was followed up and the final diagnosis for the cause of the mechanical low back pain was disc degeneration. The cause of the left SI lesion is unproven but it most likely represents a small fatigue stress reaction in association with mild osteoarthritis of the SI joint. These MRI observations are frequently seen in weight-bearing joints as they degenerate.

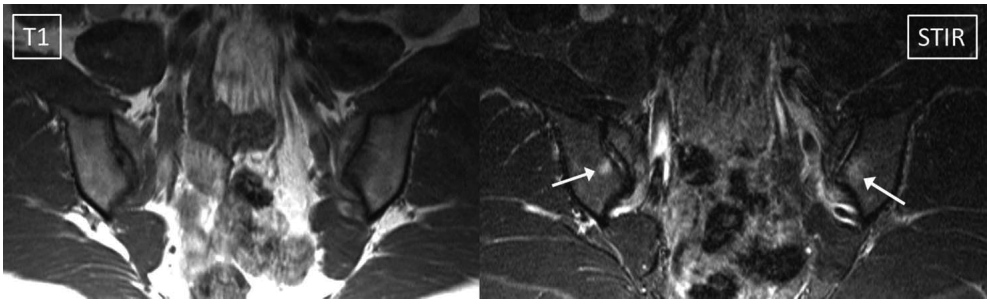


Figure 4: MRI sacroiliac (SI) joints—healthy volunteer. MRI of SI joints in a 35-year-old female health services worker who was an asymptomatic volunteer enrolled as a control subject into an ethics-approved research project. There was no history of pregnancy. The subject was fit and healthy and did not participate in any endurance activities. Clinical evaluation confirmed the absence of any symptoms, signs or risk factors for spondyloarthritis (SpA). The volunteer has been followed for 10 years and remains asymptomatic. The short tau inversion recovery (STIR) sequence shows abnormal increased signal (arrows) in the subchondral bone of both SI joints. The findings were clearly visible on at least two slices bilaterally. The lesions on STIR are small (12 mm on left and 8 mm on right) and are located close to the anterior borders of the SI joints. Some brighter signals in the 'joint space' seen on these and other images are suspicious for cartilage degeneration. Minimal signal change is present on the T1-weighted sequence and no structural damage changes are present. The follow-up MRI performed 8 weeks later as part of the clinical trial was unchanged.

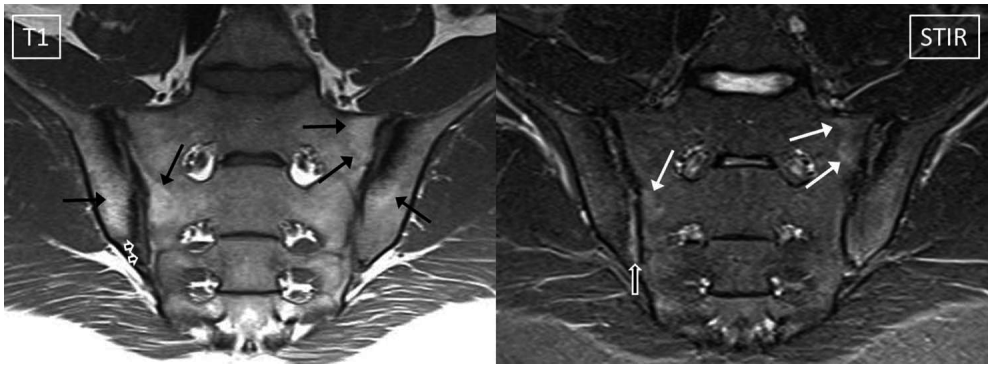


Figure 5: MRI sacroiliac (SI) joints—typical findings in non-radiographic axial spondyloarthritis (SpA) showing minimal inflammation and structural damage changes. MRI of SI joints in a 20-year-old male with inflammatory low back pain of more than 3 months duration. C-reactive protein was normal at the time of the MRI scan and HLA-B27 was positive. Pelvic radiograph was suspicious for SpA but did not meet the definition for a positive radiograph according to the modified New York criteria—right SI joint grade 2 and left SI joint grade 0. The short tau inversion recovery (STIR) sequence shows subtle increased signal (white arrows) in the subchondral bone of the right and left sacral alae suspicious for bone marrow oedema (BMO). However, the lesions are faint and heterogeneous and the right sacral lesion was only visible on one slice. If no other findings were present, it would be difficult to decide whether the BMO changes alone do or do not meet the criteria for a positive MRI. However, multiple other abnormalities are present on the MRI that materially influence the decision. On the T1-weighted sequence, subtle articular surface erosion is definitely seen at the caudal end of the right ilium (arrowheads); subtle foci of fat metaplasia are seen in all four bones (black arrows); and bilateral iliac subchondral sclerosis is present. Additionally, on the STIR sequence, abnormal increased signal overlying the area of articular surface erosion is typical for inflammation in the cartilage/joint space (compound arrow). Each finding individually is non-specific; however, in combination the appearance and distribution of all the findings are typical for inflammatory sacroiliitis. In conclusion, the MRI scan meets the Assessment in SpondyloArthritis International Society (ASAS) definition for a positive MRI because (1) BMO on STIR is present; (2) the inflammation is located in a typical anatomical area (subchondral bone) and (3) the MRI appearance is highly suggestive of SpA—in this case, because the findings of BMO are supported by MRI findings of structural damage (erosion, fat metaplasia and sclerosis) that are typical in appearance and distribution for SpA.

New data regarding the classification of patients with early axial SpA were presented from several cohorts that are currently under investigation. Using the DESIR cohort of subjects with inflammatory back pain (IBP) of less than 3 years duration before the age of 50, the reliability of classification of radiographs and MRI was compared between rheumatologists and radiologists of 25 local recruiting centres and central readers.[5-7] The results indicate that the existing MRI definition could be applied across multiple centres with the expectation of acceptable reliability and at least with better reliability than the X-ray definition of sacroiliitis according to the modified New York criteria.

A detailed analysis of SI joint MRI scans from a pair of Canadian/Swiss inception cohorts of 157 consecutive subjects ≤50 years old with back pain that included age and sex-matched controls suggests that benefit might be gained from adding SI erosion to the definition.[8]

This was observed in both non-radiographic axSpA patients with short symptom duration (mean 1.3 years) and those with longer duration (mean 10 years). However, the analysis did not take into consideration whether these subjects had or had not already met the ASAS classification for axial SpA by the clinical arm and so the incremental benefit to classification by adding erosion to the definition is not clear.

In the SPACE cohort of subjects with chronic back pain of less than 2 years duration starting before age 45, the effect of adding structural change to the definition of a positive SI joint MRI was analysed by each feature individually and in combination.[9] In this cohort, there was no single lesion or combination of lesions that would confer a significant benefit to sensitivity of the ASAS MRI definition without a corresponding risk of losing specificity.

With regard to the spine, the Canadian/Swiss inception cohorts examined the incremental value of spine MRI and concluded that while sensitivity was enhanced by 16% with combined assessment of the spine in addition to the sacroiliac joint (SIJ), false-positive diagnoses of SpA were increased by a similar degree.[10] Data were also analysed for the spine MRI in the SPACE cohort with the effect on classification of the subjects analysed by lesion type and also by the number of qualifying lesions present with a range of cut-off thresholds analysed for each lesion separately. For each type of lesion, the marginal benefit (sensitivity) for adding spine MRI to the definition comes at the price of both diminished specificity and additional financial cost.[11]

In summary, new data were presented indicating that:

- For the SI joint, the current definition of a positive MRI (active sacroiliitis) performs satisfactorily for the classification of axial SpA according to the ASAS axial SpA criteria, and can be interpreted across many centres with substantial reader agreement.
- Evaluation of structural features, especially erosions, may enhance confidence in the classification of axial SpA emphasizing the importance of simultaneous assessment of T1W and fat-suppressed sequences, and the contextual interpretation of MRI. However, the effect on classification of the addition of any structural damage feature to the definition of a positive SI joint MRI is not yet clear, in part due to variations in MRI acquisition protocol and advancing MRI technology that compounded the complexities of achieving consensus for definitions for each MRI structural damage lesion and the setting of thresholds for any defined lesion or combination of lesions.
- There is no consistent beneficial effect of adding features of SpA on spine MRI to the definition.

Following extensive discussion, the consensus opinion of the group was that 'The definition of a positive MRI should not be changed at this time. The utility of the structural damage changes of the SI joints and the addition of features on MRI of the spine for classification purposes is not yet clear and this continues to be an important research agenda'. The available data (not all data from some references were available at the time) were then presented and discussed at the annual assembly of ASAS on 17 January 2014. The meeting concluded with voting open to all members and a proposal to not change the existing definition was unanimously approved.

Definition of sacroiliitis on MRI

After deciding to not change the definition of sacroiliitis on MRI for application in the ASAS classification criteria, it was agreed by consensus to provide some clarification of the existing definition and guidelines for the application of the definition. The presentation of the existing definition was reformatted accordingly (Box 1) and guidelines for the application of the definition are now provided (Box 2).

Box 1: Definition of a positive MRI (active sacroiliitis) for the classification of axial spondyloarthritis (SpA) according to the Assessment in SpondyloArthritis International Society (ASAS) axial SpA criteria

Inflammation of the sacroiliac joints highly suggestive of SpA is required for the fulfilment of the imaging criterion 'active sacroiliitis on MRI' according to the ASAS classification criteria for axial SpA. The requirements are listed below and guidelines for the application of the definition are provided in Box 2.

REQUIRED MRI evidence of bone marrow inflammation must be present and the features required for the definition of active sacroiliitis on MRI are:

1. Bone marrow oedema (BMO) on a T2-weighted sequence sensitive for free water (such as short tau inversion recovery (STIR) or T2FS) or bone marrow contrast enhancement on a T1-weighted sequence (such as T1FS post-Gd).
2. Inflammation must be clearly present and located in a typical anatomical area (subchondral bone).
3. MRI appearance must be highly suggestive of SpA.

NOT REQUIRED Other findings related to sacroiliitis may be observed on MRI but are not required to fulfil the imaging criterion 'active sacroiliitis on MRI':

- The sole presence of other inflammatory lesions such as synovitis, enthesitis or capsulitis without concomitant BMO is not sufficient for the definition of 'active sacroiliitis on MRI'.
- In the absence of MRI signs of BMO, the presence of structural lesions such as fat metaplasia, sclerosis, erosion or ankylosis does not meet the definition of 'active sacroiliitis on MRI'.

Box 2: Guidelines for the application of the definition of a positive MRI (active sacroiliitis) for the classification of axial spondyloarthritis (SpA)

MRI interpretation:

- Bone marrow oedema (BMO) representing an inflammatory lesion that meets the above criterion will usually be easily seen on at least two consecutive slices of an MRI scan. Detection of inflammation on a single slice may be sufficient for the criterion 'highly suggestive of SpA' if there is more than one inflammatory lesion present. However, it is rare for an MRI scan of the sacroiliac joints with definite evidence of active sacroiliitis to demonstrate lesions on only a single image, and caution should be exercised in the interpretation of small lesions.
- It is essential that the reader of the MRI scan simultaneously review sequences designed to identify inflammation and sequences that focus on depiction of structural damage.
- If an inflammatory bone marrow lesion appears to be present but it is hard to determine whether the lesion meets the criterion 'highly suggestive of SpA', then the decision may be influenced by the presence of concomitant structural damage, especially erosion, and/or other signs of inflammation, which in themselves do not suffice to meet the criterion.

Context:

- Evaluation of an MRI scan should be performed objectively. However, MRI findings are non-specific and the determination of the importance of the observations should never be made in isolation of the clinical context as demographic, clinical and laboratory information may outweigh the importance of the MRI findings.
- The definition and guidelines are primarily for the classification of patients with SpA and will not be suitable for use in some clinical situations.

DISCUSSION

The ASAS/OMERACT MRI working group previously decided by consensus that the presence of subchondral BMO (or osteitis) in the SI joints reflecting inflammation highly suggestive of SpA should be regarded as essential to meet the definition of 'active sacroiliitis on MRI' in cases of axial SpA when radiographic changes are absent or doubtful.[3] The purpose of this consensus exercise was to examine whether new data published in the last 5 years regarding axial SpA are sufficient to merit a change in the MRI definition of a positive MRI and clarify any misunderstanding of the existing definition that may have become apparent since its first publication. After detailed consideration, the unanimous consensus of ASAS members was to retain the existing definition with a slight rewording that would help to emphasise the critical components of the definition.

The ASAS definition of 'active sacroiliitis on MRI' was the first definition of 'a positive MRI' to be widely used in clinical trials research. The development of the definition was based on published data and took other factors into consideration: universal agreement that, above all, MRI evidence of inflammation (which is radiographically occult) must be included in a

definition of non-radiographic disease; easily applied MRI parameters; ability to apply the definition prospectively and retrospectively; and wording and illustration of the definition that was simple and intuitive. Ease of application of the criteria internationally is important and the minimum MRI technical requirements can be applied on any MRI platform and do not change with advancing technology. A wide range of newer sequences such as water excitation or chemical shift imaging may be used to detect bone marrow inflammation but do not change the principles of image acquisition or the definition of 'active sacroiliitis'. Most centres use either STIR or T2FS as in most cases, T1-weighted contrast-enhanced sequences offer no additional benefit in either adults or children and contrast material is expensive and is therefore not recommended.[12-15]

The selection of an MRI definition is influenced by how it performs in a rigorous testing environment and by the ability to describe and illustrate the target lesion in terms that facilitate widespread application. This is another reason that the ASAS definition remains focused on the inflammatory lesion in the SI joint at this time and why structural damage lesions have not yet been added to the definition. Erosion of the joint surface may seem to be a logical choice for inclusion in a definition of sacroiliitis; however, currently, there is no international consensus as to how erosion should be defined on MRI or how it should be quantified. For example, it is not yet clear to what extent variation in MRI acquisition parameters, such as using a thin-slice high-resolution three-dimensional sequence, would alter the properties of a definition that includes structural damage. Features of axial SpA identifiable on spine MRI are still not included in the definition of a positive MRI because none of the candidate definitions would appear to confer a significant advantage over the current definition. The SI joints are involved before the spine in the majority of true axial SpA cases and the matter is complicated by the fact that degenerative changes in the spine are frequent and small foci of inflammation that are mechanical in origin may be indistinguishable from small inflammatory lesions due to SpA.[10,16]

The European Society of Skeletal Radiology (ESSR) recently reviewed the imaging appearances and the radiological features necessary for making a diagnosis of axial SpA and recommended that MRI is mandatory to look for early inflammatory lesions if axial SpA is suspected and radiographs are negative.[17] The burden of disease required to meet a diagnosis of sacroiliitis described by the ESSR Arthritis Imaging Subcommittee is consistent with the ASAS definition for classification, which requires all lesions to be 'highly suggestive of SpA'. It should be noted that the ESSR publication omits quotation of this critical component of the ASAS definition. In the case of minimal inflammatory changes, specific advice regarding the exact nature and extent of additional imaging features of SpA that would be required to heighten the suspicion of the observer is not provided and this remains an important focus

for future research. As noted previously, doubtful cases of BMO should not be considered as positive, and this view is supported by data highlighting the prognostic role of more extensive BMO for the later development of radiographic sacroiliitis.[18]

The publication by ASAS of the first 'definition of active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis' was an important step that has enabled many subsequent research projects. The existing definition is based on the observance of inflammatory lesions in typical locations related to the SI joint and can be applied by readers across the world with access to any MRI unit. The ASAS definition was reviewed by an expert group of rheumatologists and radiologist with experience in both SpA and MRI including systematic analysis of data from different cohorts. The results were presented by experts to the ASAS members. By a final vote of all members, the unanimous consensus was to retain the existing definition with a slight rewording that would help to emphasise the critical components of the definition. The contribution of MRI features of structural damage of the SI joint or spinal MRI features of SpA to a refined classification of axial SpA remains an important research agenda. However, the existing ASAS definition of a positive MRI continues to provide a solid basis for the application of MRI in the ASAS criteria for axial SpA.

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6

Can we use structural lesions seen on MRI of the sacroiliac joints reliably for the classification of patients according to the ASAS axial spondyloarthritis criteria? Data from the DESIR cohort

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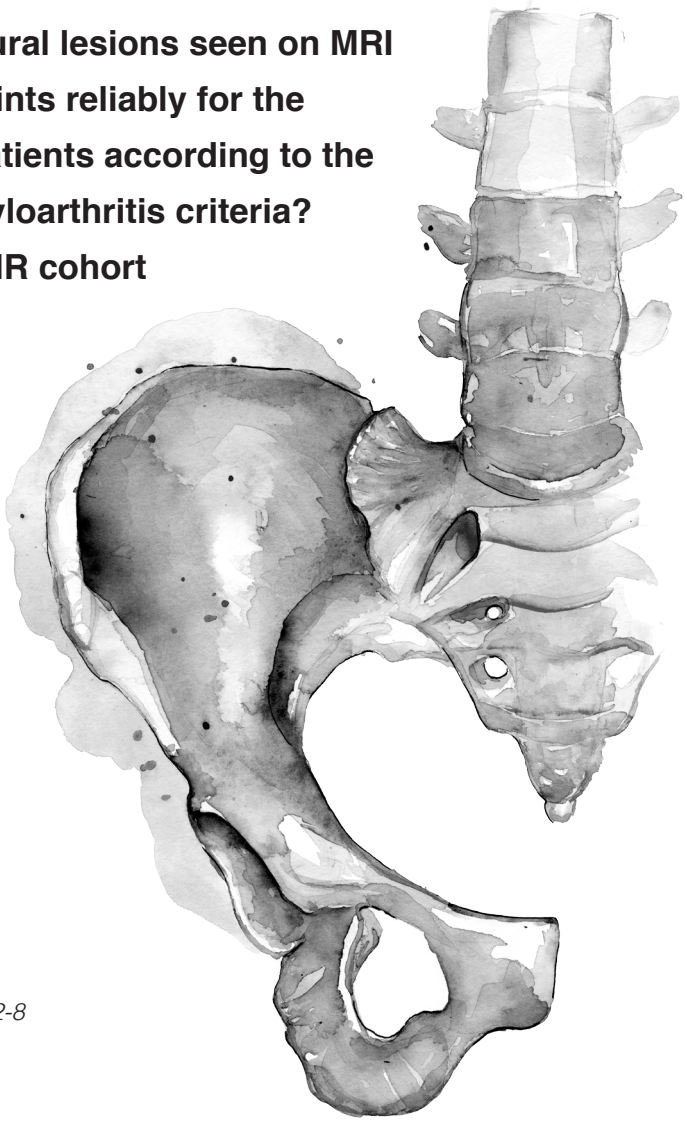

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ABSTRACT

Objective

Investigating the utility of adding structural lesions seen on MRI of the sacroiliac joints to the imaging criterion of the Assessment of SpondyloArthritis (ASAS) axial SpondyloArthritis (axSpA) criteria and the utility of replacement of radiographic sacroiliitis by structural lesions on MRI.

Methods

Two well-calibrated readers scored MRI STIR (inflammation, MRI-SI), MRI T1-w images (structural lesions, MRI-SI-s) and radiographs of the sacroiliac joints (X-SI) of patients in the DEvenir des Spondyloarthrites Indifférenciées Récentes cohort (inflammatory back pain: ≥3 months, <3 years, age <50). A third reader adjudicated MRI-SI and X-SI discrepancies. Previously proposed cut-offs for a positive MRI-SI-s were used (based on <5% prevalence among no-SpA patients): erosions (E) ≥3, fatty lesions (FL) ≥3, E/FL ≥5. Patients were classified according to the ASAS axSpA criteria using the various definitions of MRI-SI-s.

Results

Of the 582 patients included in this analysis, 418 fulfilled the ASAS axSpA criteria, of which 127 patients were modified New York (mNY) positive and 134 and 75 were MRI-SI-s positive (E/FL≥5) for readers 1 and 2, respectively. Agreement between mNY and MRI-SI-s (E/FL≥5) was moderate (reader 1: κ: 0.39; reader 2: κ: 0.44). Using the E/FL≥5 cut-off instead of mNY classification did not change in 478 (82.1%) and 469 (80.6%) patients for readers 1 and 2, respectively. Twelve (reader 1) or ten (reader 2) patients would not be classified as axSpA if only MRI-SI-s was performed (in the scenario of replacement of mNY), while three (reader 1) or six (reader 2) patients would be additionally classified as axSpA in both scenarios (replacement of mNY and addition of MRI-SI-s). Similar results were seen for the other cut-offs (E≥3, FL≥3).

Conclusions

Structural lesions on MRI can be used reliably either as an addition to or as a substitute for radiographs in the ASAS axSpA classification of patients in our cohort of patients with short symptom duration.

INTRODUCTION

A commonly used imaging method for the assessment of sacroiliitis is conventional radiography. Radiographic sacroiliitis is obligatory in the modified New York (mNY) criteria for ankylosing spondylitis (AS).[1] However, it has been shown that it is very difficult to reliably detect sacroiliitis on conventional radiographs. Substantial observer variation exists for both radiologists and rheumatologists, which can lead to substantial misclassification of patients.[2] Moreover, it has been shown that training in the reading of these radiographs does not lead to improvement.[3]

Another downside of conventional radiography is that only structural damage in the sacroiliac joints can be detected, frequently appearing after several years of disease, which hampers early detection. MRI can reliably detect inflammation of the sacroiliac joints at an early stage before damage on radiographs can be detected.[4] Sacroiliitis on MRI plays an important role in the imaging arm of the Assessment of SpondyloArthritis (ASAS) axial SpondyloArthritis (axSpA) criteria.[5]

Besides inflammatory lesions, structural lesions such as erosions, fatty lesions, sclerosis and ankylosis are visible on MRI. Therefore, MRI has great potential for the assessment of both active inflammatory lesions and structural damage by means of one single-imaging technique. In the recently published European League Against Rheumatism (EULAR) recommendations for the use of imaging in the diagnosis and management of axSpA in clinical practice, it was advocated to take structural lesions (such as bone erosion, fat infiltration, sclerosis and new bone formation) into account in addition to active inflammatory lesions.[6] This is augmented by accruing worries about radiation exposure coupled with conventional radiographs in some parts of the world.

By this study, we aim to further clarify the role of these structural lesions and to investigate their usefulness with regard to the ASAS axSpA classification of patients. First, we determine the agreement between the presence of sacroiliitis on radiographs (mNY criteria) and structural lesions seen on MRI. Subsequently, we evaluate what impact the use of structural lesions on MRI-SI could have on the performance of the ASAS axSpA criteria. Two scenarios are investigated: the addition of structural lesions seen on MRI to the definition of 'sacroiliitis on imaging' (scenario 1) and the replacement of radiographic sacroiliitis by structural lesions on MRI (scenario 2). For both scenarios, the impact on the classification of patients according to the ASAS axSpA criteria is assessed.

METHODS

Study population

Baseline data from the DEvenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort were used for this analysis. The DESIR cohort has been extensively described before.[7] In short, the DESIR cohort is a French prospective longitudinal cohort study following 708 patients (aged >18 years and <50 years) over time with inflammatory back pain (IBP) for ≥3 months and <3 years, located in the thoracic spine, lumbar spine and/or buttock area. IBP was defined according to either the Calin or Berlin criteria.[8,9] Patients were included only in case of a suspicion of SpA, according to the rheumatologist defined as a score ≥5 on a 0–10 scale (0: not suggestive of axSpA and 10: very suggestive of axSpA). All patients underwent a full diagnostic work-up including MRI and conventional radiographs of the sacroiliac joints (MRI-SI and X-SI, respectively), HLA-B27 testing and the assessment of all other SpA-features, in agreement with the descriptions provided by ASAS.[5] Inclusion was performed in 25 centres across France and took place between December 2007 and April 2010. The database for the baseline data used for this analysis was locked on 30 October 2012. The study fulfilled Good Clinical Practice Guidelines and was approved by the appropriate medical ethical committees. Patients gave informed consent before start of the study.

Imaging and scoring methods

MRI of the sacroiliac joints (MRI-SI) was performed at baseline, in each participating centre, on 1.0–1.5 T machines. The acquired sequences were coronal oblique T1-weighted FSE and STIR with 12–15 semi-coronal slices of 4 mm thickness, parallel to the long axis of the sacrum. Plain radiographs of the pelvis (X-SI) were performed at baseline, in anteroposterior view. All available MRI-SIs and X-SIs were read by two well-calibrated readers (MRI: FT and RvdB and X-SI: GL and RvdB) independently, in different reading sessions. The reading process was completely blinded: readers had no insight in patient characteristics and other clinical and imaging data. The training and calibration process of the different readers was extensively described before.[2]

Sacroiliitis on radiographs was assessed according to the mNY criteria; radiographic sacroiliitis was defined as bilateral grade ≥2 or unilateral grade ≥3.[1] Regarding the presence of inflammatory lesions on MRI-SI, the ASAS definition for a positive MRI-SI was used. An MRI-SI was marked positive if one bone marrow oedema (BME) lesion highly suggestive of SpA was present on ≥2 consecutive slices or alternatively if several BME lesions highly suggestive of SpA were visible on a single slice.[4] The presence of structural lesions on MRI-SI was assessed using different types of lesions: fatty lesions, erosions, sclerosis, (partial) ankylosis.

We used a scoring system with similarities to the methodology outlined in the SPARCC online training module, as described by Weber et al in 2010, to assess MRI-SI on the presence of structural lesions.[10] In contrast to the SPARCC method, the scoring method we used is purely based on counting the number of structural lesions. Each SI joint is divided into quadrants. The presence of structural lesions was assessed (present vs absent) in each quadrant on six consecutive slices through the SI joints; starting on the slice on which at least 1 cm of vertical height of the cartilage compartment is visible, from anterior to posterior, assessing the cartilaginous compartment of the SI joints and the anteroinferior portion of the SI joint. Structural lesions were only considered present if seen on at least two consecutive slices, resulting in a maximum score of 40 per lesion (5 per quadrant (as a lesion needs to be visible on two consecutive slices)× 4 quadrants× 2 sacroiliac joints) except for (partial) ankylosis. It was considered sufficient if (partial) ankylosis was seen on a single slice and since ankylosis involves always a sacral and an iliac part, the maximum score results in 24. More information about the scoring method for structural lesions is given in Supplementary Table 1.

Structural lesions on MRI-SI were assessed by two readers, without the use of an adjudicator. Therefore, results were analysed separately per reader. In contrast, regarding the presence of sacroiliitis on radiographs (mNY) and inflammation on MRI-SI (ASAS definition) adjudicator scores (MR) were available.

Assessment of structural lesions

Recently, definitions for a positive MRI for structural lesions (MRI-SI-s) using different cut-offs of various structural lesions were proposed by de Hooge et al.[11] This was done in the SPondyloArthritis Early Cohort (SPACE): a cohort similar to the DESIR cohort, but slightly different since patients with chronic back pain (CBP) were included and not only patients with IBP and, more importantly, in SPACE also patients without a high suspicion of SpA were included.

The cut-offs were based on ≤5% false positives whereby the false positives were defined as structural lesions among patients with a very low likelihood of axSpA.[11] These cut-offs are as follows: 'erosions ≥3', 'fatty lesions ≥3', 'fatty lesions and/or erosions ≥5'. Prevalence of sclerosis and ankylosis was so low that there was not a cut-off that could clearly distinguish between SpA and no-SpA patients. Therefore, these types of lesions were not taken into account any further.

Classification criteria

The ASAS axSpA criteria were used for classification of patients. Patients were grouped based on how they fulfilled the criteria: via the imaging arm of the ASAS axSpA criteria (either by fulfilling mNY criteria and/or positive MRI); via the clinical arm of the ASAS axSpA criteria;

or via both. If patients fulfilled several categories, they were classified as such, resulting in seven possible combinations (Tables 3 and 4). Patients not fulfilling the ASAS axSpA criteria were grouped into the no-axSpA group. It is important to realise that patients that have multiple axSpA features present but formally not fulfil the ASAS axSpA criteria (since they are mNY-negative, MRI-negative and HLA-B27-negative) are also included in this group.

Data analysis

Disease characteristics of patients included in the DESIR cohort were presented using descriptive statistics. Agreement on the absence or presence of structural lesions using both imaging modalities (X-SI and MRI-SI-s) was assessed by cross-tabulation and expressed as Cohen's κ. In order to disregard subjects labelled as negative by both readers, which can make agreement look artificially high, percentage agreement on the positive cases (positive agreement) was calculated.[12] Both measures of agreement were also calculated for the concordance between radiographic sacroiliitis on conventional radiographs and a positive MRI-SI-s (per individual reader). Radiographic sacroiliitis (present vs absent) was based on the mNY criteria and MRI-SI-s for structural lesions was based on the proposed cut-offs for a positive MRI-SI-s.

Subsequently, patients were classified according to the ASAS axSpA criteria, using the various definitions of MRI-SI-s. First, MRI-SI-s was added to the imaging criterion of the ASAS axSpA criteria as an additional possibility to fulfil the imaging arm (scenario 1). Second, the mNY criterion was replaced by MRI-SI-s (scenario 2, as if only an MRI was available). For patients that newly fulfilled the ASAS axSpA criteria in scenario 1 and whom ASAS axSpA classification changed by scenario 2, the probability of having axSpA was calculated by the positive likelihood ratio (LR+) product. This was done by multiplying the individual LRs of all present SpA features in a patient.[13] For example, an LR product of 200 results in a positive predictive value of 90% in patients with CBP with an assumed pre-test disease prevalence of axSpA of 5%.[14] The analyses were performed in STATA V.12.0.

Table 1: Disease characteristics of the patients included in the analyses

	Total number of patients (n=582)
Age (years) at inclusion, mean ±SD	31.5 (7.2)
Male, n (%)	297 (51.0)
Symptom duration (months) at first visit, mean ±SD	18.2 (10.6)
HLA-B27 positive, n (%)	338 (58.1)
Positive family history SpA, n (%)	146 (25.1)
IBP, n (%)	582 (100)
Psoriasis, n (%)	90 (15.5)
Dactylitis, n (%)	74 (12.7)
Enthesitis, n (%)	282 (48.5)
Uveitis, n (%)	40 (6.9)
IBD, n (%)	29 (5.0)
Elevated CRP, n (%)	168 (30.6)
Good response to NSAIDs, n (%)	459 (78.9)
Peripheral arthritis, n (%)	100 (17.2)
Sacroiliitis present on radiograph, n (%)	126 (21.6)
Positive MRI (ASAS definition), n (%)	210 (36.1)

HLA-B27, human leukocyte antigen B27; IBP, inflammatory back pain; IBD, inflammatory bowel disease; CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs, MRI, magnetic resonance imaging; ASAS, Assessment of SpondyloArthritis international Society.

RESULTS

In total, 582 patients with complete imaging data (both MRI-SI and X-SI present), evaluated by two readers, were included in this analysis. Disease characteristics are depicted in Table 1. The mean age was 31.5 years (SD 7.2 years) and 51% were male. Patients had a mean duration of back pain of 18.2 months (SD 10.6 months) and 338 patients (58.1%) were HLA-B27 positive. Fulfilment of the ASAS axSpA criteria was seen in 418 (71.8%) patients (while using adjudicated scores and based on the original definition of imaging).

As published before, agreement between the two readers regarding the absence/presence of radiographic sacroiliitis (mNY) is moderate: κ 0.54.[2] Regarding the definition of a positive MRI-SI according to the ASAS definition, inter-reader agreement was much better: κ 0.73.[15] Inter-reader agreement between readers 1 and 2 was calculated for the various structural lesions definitions. The agreement on the presence of ≥3 erosions was poor: κ 0.19. For the presence of fatty lesions and the combination of fatty lesions/erosions, it was somewhat better, κ 0.50 and κ 0.44, respectively. Subsequently, agreement between radiographic sacroiliitis (mNY criteria) and a positive MRI-SI-s (using the various cut-offs) was assessed. Agreement was rather low and varied between κ 0.21 and κ 0.44 (Table 2).

Table 2: Agreement between sacroiliitis on conventional radiographs (modified New York criteria) and a positive MRI-SI based on structural lesions

	Reader 1				
	X-SI (adjudicated score)				
MRI-SI	Erosions: cut-off ≥3		modified New York criteria		**κ: 0.21**
			Positive	Negative	Total
		Positive	22	10	32
		Negative	105	444	549
		Total	127	454	581*
			Positive agreement: 16.1%		
	Fatty lesions: cut-off ≥3		modified New York criteria		**κ: 0.39**
			Positive	Negative	Total
		Positive	53	34	87
		Negative	74	420	494
		Total	127	454	581
			Positive agreement: 32.9%		
	Erosions/fatty lesions: cut-off ≥5		modified New York criteria		**κ: 0.39**
			Positive	Negative	Total
		Positive	49	26	75
		Negative	78	428	506
		Total	127	454	581
			Positive agreement: 32.0%		
	Reader 2				
	X-SI (adjudicated score)				
MRI-SI	Erosions: cut-off ≥3		modified New York criteria		**κ: 0.39**
			Positive	Negative	Total
		Positive	68	63	131
		Negative	59	391	450
		Total	127	454	581
			Positive agreement: 35.8%		
	Fatty lesions: cut-off ≥3		modified New York criteria		**κ: 0.40**
			Positive	Negative	Total
		Positive	61	47	108
		Negative	66	407	473
		Total	127	454	581
			Positive agreement: 35.1%		
	Erosions/fatty lesions: cut-off ≥5		modified New York criteria		**κ: 0.44**
			Positive	Negative	Total
		Positive	74	60	134
		Negative	53	394	447
		Total	127	454	581
			Positive agreement: 39.6%		

*Note: in this table 581 patients are included (total number of included patients in the study being 582) since the T1-sequence MRI was missing in one patient (STIR-sequence available).
X-SI, conventional radiographs of the sacroiliac joints; MRI-SI, magnetic resonance imaging of the sacroiliac joints.

Table 3: Scenario 1: *Addition* of MRI-SI-s to the ASAS axSpA-criteria (≥5 erosions/fatty lesions) reader 1/*reader 2*

		ASAS axSpA classification criteria								
		Negative	Only clinical arm positive	Only MRI active positive	Only mNY positive	Clinical arm and MRI active positive	Clinical arm and mNY positive	Clinical arm, MRI active positive, mNY positive	Both MRI active and mNY positive	**Total**
ASAS axSpA-criteria: **addition of MRI-SI-s**	Negative	161/*158*								**160/*157***
	Only clinical arm positive	0	169/*162*							**169/*162***
	Only MRI active positive	0	0	42/*34*						**42/*34***
	Only MRI-SI-s/mNY positive	3/*6*	0	0	13/*13*					**16/*19***
	Clinical arm and MRI active positive	0	0	0	0	57/*41*				**57/*41***
	Clinical arm and MRI-SI-s/mNY positive	0	7/*14*	0	0	0	19/*19*			**26/*33***
	Clinical arm, MRI active and MRI-SI-s/mNY positive	0	0	0	0	8/*24*	0	77/*77*		**85/*101***
	MRI active and MRI-SI-s/mNY positive	0	0	8/*16*	0	0	0	0	18/*18*	**26/*34***
	Total	**164/*164***	**176/*176***	**50/*50***	**13/*13***	**65/*65***	**19/*19***	**77/*77***	**18/*18***	582/*582*

Classification remains the same

mNY- patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY- patients not fulfilling the ASAS axSpA-criteria, became ASAS axSpA positive based on MRI-SI-s+

Not possible in this scenario

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

Scenario 1

First, we investigated the effect of adding MRI-SI-s to the imaging criterion of the ASAS axSpA criteria (Table 3) . Using a cut-off value of 5 for the combination of 'fatty lesions and/or erosions', classification did not change in the majority of the patients: 556 patients (95.5%) and 522 patients (89.7%) for readers 1 and 2, respectively. Regarding the combination of 'fatty lesions and/or erosions', three or six patients (readers 1 and 2, respectively) would be additionally classified as axSpA if structural lesions on MRI were taken into account (two patients, identified by both readers). Only two of these in total seven patients presented with four SpA features in addition to IBP, which was present in all cases. None of these patients was HLA-B27 positive. The LR+ products varied between 3 and 968, respectively, corresponding to post-test probabilities of 13% and 98%. A post-test probability of >80% was seen in one patient only. Similar results were found when using a cut-off for 'fatty lesions' only and 'erosions' only (both cut-off values of 3) (Supplementary Table 2 and Supplementary Table 4).

More patients did not gain an ASAS classification by applying MRI-SI-s, but changed subgroups within the ASAS axSpA criteria. Regarding the combination of 'fatty lesions and/or erosions', 23 (reader 1) and 54 (reader 2) patients would be classified via different arms due to the presence of structural lesions on MRI-SI. Also, 16 or 40 patients (reader 1 or reader 2) were already classified via the imaging arm based on inflammatory lesions on MRI and also showed structural lesions on MRI (Table 3) with or without fulfilment of the clinical arm. And, 7 or 14 other patients (reader 1 or reader 2) fulfilled the clinical arm only, but fulfilled the imaging arm too based on a positive MRI-SI-s. The same trends were seen when using a cut-off for 'fatty lesions' only and 'erosions' only (both cut-off values of 3) (Supplementary Table 2 and Supplementary Table 4).

Scenario 2

Second, we assessed whether replacing radiographic sacroiliitis by structural lesions on MRI (Table 4) had an impact on ASAS classification. Using the same cut-off values of 5 for the combination of 'fatty lesions and/or erosions', classification did not change in the majority of the patients (82.1% and 80.6% for readers 1 and 2, respectively). A similar result was seen using a cut-off value of 3 for 'erosions' and 'fatty lesions' only: classification did not change in 80.2% or 79.0% (readers 1 and 2) and 81.4% or 80.6% of the patients, respectively (Table 5). Comparing results of the two readers, differences were seen among them, but these changes mainly involve shifts between the different arms within the ASAS axSpA criteria rather than changes in ASAS axSpA classification (yes/no) in general (Table 5). Similar results were found when using a cut-off for 'fatty lesions' only and 'erosions' only (both cut-off values of 3) (Supplementary Table 3 and Supplementary Table 5).

Table 4: Scenario 2: *Replacing mNY-criteria* by MRI-SI-s in the ASAS axSpA classification (≥5 erosions/fatty lesions) reader 1/*reader 2*

	ASAS axSpA classification criteria	Negative	Only clinical arm positive	Only MRI active positive	Only mNY positive	Clinical arm and MRI positive	Clinical arm and mNY positive	Clinical arm, MRI active positive, mNY positive	Both MRI active and mNY positive	**Total**
ASAS axSpA-criteria: **replacement of X-SI by MRI-SI-s**	Negative	161/*158*	0	0	12/*10*	0	0	0	0	**173/*168***
	Only clinical arm positive	0	169/*162*	0	0	0	9/*9*	0	0	**178/*171***
	Only MRI active positive	0	0	42/*34*	0	0	0	0	13/*9*	**55/*43***
	Only MRI-SI-s positive	3/*6*	0	0	1/*3*	0	0	0	0	**4/*9***
	Clinical arm and MRI active positive	0	0	0	0	57/*41*	0	44/*25*	0	**101/*66***
	Clinical arm and MRI-SI-s positive	0	7/*14*	0	0	0	10/*10*	0	0	**17/*24***
	Clinical arm, MRI active and MRI-SI-s positive	0	0	0	0	8/*24*	0	33/*52*	0	**41/*76***
	MRI active and MRI-SI-s positive	0	0	8/*16*	0	0	0	0	5/*9*	**13/*25***
	Total	**164/*164***	**176/*176***	**50/*50***	**13/*13***	**65/*65***	**19/*19***	**77/*77***	**18/*18***	**582/*582***

Classification remains the same

mNY- patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY- patients not fulfilling the ASAS axSpA-criteria, became ASAS axSpA positive based on MRI-SI-s+

mNY+ patients became MRI-SI-s-, but remained classified ASAS axSpA positive

mNY+ patients became ASAS axSpA-criteria negative because of MRI-SI-s-

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

Table 5: Scenario 2: Changes in ASAS axSpA-classification, using all three combinations of lesions

Reader 1			
	Erosions ≥3	Fatty lesions ≥3	Erosions and/or fatty lesions ≥5
Classification remained the same	467 (80.2%)	474 (81.4%)	478 (82.1%)
mNY+ patients with MRI-SI-s-, but remained ASAS+	92 (15.8%)	62 (10.6%)	66 (11.3%)
mNY- patients with structural lesions on MRI, within ASAS+	9 (1.5%)	30 (5.2%)	23 (4.0%)
ASAS- patients based on mNY- became ASAS+ based on MRI-SI-s+	1 (0.2%)	4 (0.7%)	3 (0.5%)
ASAS+ patients based on mNY+ became ASAS- based on MRI-SI-s-	13 (2.2%)	12 (2.1%)	12 (2.1%)
Total	582	582	582
Reader 2			
	Erosions ≥3	Fatty lesions ≥3	Erosions and/or fatty lesions ≥5
Classification remained the same	460 (79.0%)	469 (80.6%)	469 (80.6%)
mNY+ patients with MRI-SI-s-, but remained ASAS+	49 (8.4%)	56 (9.6%)	43 (7.4%)
mNY- patients with structural lesions on MRI, within ASAS+	51 (8.8%)	41 (7.0%)	54 (9.3%)
ASAS- patients based on mNY- became ASAS+ based on MRI-SI-s+	12 (2.1%)	6 (1.0%)	6 (1.0%)
ASAS+ patients based on mNY+ became ASAS- based on MRI-SI-s-	10 (1.7%)	10 (1.7%)	10 (1.7%)
Total	582	582	582

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

In this scenario, of course, the same patients would be additionally classified as axSpA as in scenario 1. But in contrast to scenario 1, now patients can also no longer fulfil the ASAS axSpA criteria. Using the combination of 'fatty lesions and/or erosions', 12 and 10 patients (2.1% and 1.7% for readers 1 and 2, respectively) would not be classified axSpA anymore if radiographic sacroiliitis was replaced by structural lesions on MRI, for example, assuming that only an MRI was available. In total and between brackets for the individual readers separately, 89 (66+23) and 97 (43+54) patients changed arms within the criteria using the combined cut-off of 'fatty lesions and/or erosions' (Table 4: yellow and orange boxes). However, all those patients were still classified axSpA.

The clinical phenotype of the patients that are no longer classified by the ASAS axSpA criteria was assessed. The same 10 patients were captured by both readers: all HLA-B27 and the number of present SpA features varied between 1 (only IBP) and 4 (IBP, peripheral

arthritis, enthesitis, dactylitis). The LR+ products varied between 3 and 190, corresponding with disease probabilities of 13% and 90%, respectively. A post-test probability of >80% was seen in two patients. The two additional patients that no longer fulfilled the ASAS axSpA criteria by reader 1 only, showed both a good response to non-steroidal anti-inflammatory drugs and one presented with enthesitis as well (corresponding to disease probabilities of 45% and 74%). Similar results were found when using a cut-off for 'fatty lesions' only and 'erosions' only (Supplementary Table 3 and Supplementary Table 5).

DISCUSSION

When sacroiliitis on radiographs was replaced by structural lesions on MRI, only minor changes in the classification according to the ASAS axSpA criteria were seen. Most patients change from one subcategory to another subcategory, rather than becoming ASAS axSpA criteria positive or negative. This adds to the robustness of the ASAS axSpA criteria as a whole.

Based on these data, if a T1-sequence MRI is available, but a pelvic radiograph is lacking, this MRI may suffice and there no reason of always obtaining additional radiographs. MRI can be therefore a reasonable alternative for radiographs since this prevents radiation exposure. More generally, our results are in line with the recent published EULAR recommendations for the use of imaging in the diagnosis and management of SpA in clinical practice, stating that on MRI both active inflammatory lesions (primarily BME) and structural lesions (such as bone erosions, new bone formation, sclerosis and fat infiltration) should be considered.[6] Nevertheless, it is important to stress the difference between that publication and the current study: the EULAR recommendations are aimed for diagnosis and in the current study we look at the ASAS axSpA classification.

As described earlier, the recognition of radiographic sacroiliitis is challenging. Unfortunately, agreement on structural lesions was only fair–moderate as well. However, it is reassuring to see that the same conclusions (effects on ASAS axSpA classification) can be drawn while comparing the data of the individual readers. This strengthens our findings and adds to the validity of the criteria itself since the results seem not too much affected to inter-reader variation in this respect. This in contrast to the mNY criteria that immediately change in case of discrepant readings. We know from earlier studies that training does not improve recognition of radiographic sacroiliitis.[3] The question whether training ameliorates recognition of structural lesions on MRI was not addressed in this study and could be relevant for future studies.

To our knowledge, the replacement of conventional radiographs by structural lesions on MRI in itself, and the effects on the ASAS axSpA classification have never been investigated before. However, data on the recognition and reliability of structural lesions visible on MRI-SI in general are available. In 2009, ASAS experts defined structural damage lesions of the sacroiliac joints on MRI. Subsequently, reliability of their detection has been studied. Weber et al found that erosions can be reliably detected on MRI to a comparable degree of reliability as BME (κ: 0.72).[16] Regarding the detection of fatty lesions, lower κ values were shown in the same paper (κ: 0.55).[16] More recently, the SPARCC SSS score was developed by the Canada–Denmark study group.[17] Recent data from a collaboration between two research groups (from Edmonton, Canada, and Leiden, the Netherlands) have shown that the presence and extent of erosions and fat metaplasia can be reliably assessed by readers from these different centres (intraclass correlation coefficient (ICC): 0.60 and 0.65, respectively), even without calibration.[18] Interobserver reliability for status scores was good for fat metaplasia (ICC: 0.71–0.78) and moderate to good for erosions (ICC: 0.58–0.62) for different reader pairs. In this study, we found a lower agreement compared with data from other studies. However, a clear comparison between reliability data of different groups is hampered by variability in study design such as inclusion criteria of the cohorts and slightly different scoring methods. Hypothesising about this, it could be plausible that patients with a short symptom duration, like in our early cohort, usually have less structural damage and that recognition of structural lesions is more challenging in a cohort of patients with early disease. Therefore, the agreement on positive imaging presented in this study might be slightly worse than could be expected in more established disease.

In the current study, we investigated the effect of using different combinations of structural lesions (fatty lesions, erosions and a combination of fatty lesions and erosions) on the classification of patients with axSpA. We could debate on the choice for the ideal cut-off and corresponding structural lesion. In this study, we found worse agreement for erosions alone and better agreement for the combination of erosions/fatty lesions and fatty lesions alone. Despite similar effects on the ASAS classification of patients, personally we prefer using a combination of fatty lesions and/or erosions instead of fatty reasons alone for reasons of face validity. But a definition based on erosions only could be a viable option too.

Although our data look promising, we should be cautious with generalising conclusions and results should be placed into perspective carefully. Before any decision can be taken on eventually leaving conventional radiographs behind, more evidence is needed since this is a decision with possibly far-reaching consequences. MRI is an expensive tool and might not be available throughout all parts of the world, which can lead to feasibility problems. Besides this, rheumatologists and radiologists worldwide are familiar with the mNY criteria. We should especially be cautious to generalise results of these data to patients with long-

standing disease since we only tested this hypothesis in one cohort with early disease. The ideal cut-off could be different in patients with longer symptom duration and more structural lesions in the sacroiliac joints. Therefore, more data are warranted and confirmation of these results is needed first, especially in cohorts of patients with established disease.

Replacement of sacroiliitis on radiographs by structural lesions on MRI is resulting in a loss of a small number of patients (scenario 2). And these patients showed a low likelihood of axSpA based on the SpA features present. Nevertheless, for the reasons explained above, we favour (for the time being) addition of structural lesions on MRI to the ASAS axSpA classification (scenario 1) instead of replacement of conventional radiographs.

Strengths of our study are the intensive scoring process by multiple readers, which adds to the credibility of our findings and the cohort itself. The DESIR cohort is a cohort of early disease, with a substantial number of patients. In general, the urge for sensitive and specific imaging tools is an emerging issue in the field of early axSpA. Besides strengths of the study, we would like to address some limitations. An important limitation of this study is the lack of a gold standard to assess structural changes in the sacroiliac joint by means of CT. Another limitation of this study is that only patients with a short disease duration are included in the DESIR cohort and that we in general see a limited number of patients with structural lesions. Therefore, hesitation is needed in order to prevent drawing definite conclusions about the use of MRI-SI-s for the definition of sacroiliitis on imaging in the ASAS axSpA criteria.

To conclude, assessment of structural lesions on MRI instead of or in addition to conventional radiographs does not lead to a different ASAS axSpA classification in the large majority of patients with IBP. Although these findings are promising, replication in other cohorts is awaited.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Scoring method for the assessment of structural lesions on MRI-SI (MRI-SI-s)

A. Maximum score that can be obtained for scoring erosions, fatty lesions and sclerosis separately:

		Left SI-joint Quadrant:				Right SI-joint Quadrant:			
		1	*2*	*3*	*4*	*1*	*2*	*3*	*4*
Lesion scored on which slices?	Slice 1 and 2	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
	Slice 2 and 3	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
	Slice 3 and 4	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
	Slice 4 and 5	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
	Slice 5 and 6	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1
	Total score	0-5	0-5	0-5	0-5	0-5	0-5	0-5	0-5
	Total score per SI-joint	0-20				0-20			
	Total score (both SI-joints)	0-40							

B. Maximum score that can be obtained for scoring partial ankylosis and ankylosis:

		Left SI-joint		Right SI-joint	
		*Quadrant 1 and 2**	*Quadrant 3 and 4**	*Quadrant 1 and 2**	*Quadrant 3 and 4**
Lesion scored on which slices?	Slice 1	0-1	0-1	0-1	0-1
	Slice 2	0-1	0-1	0-1	0-1
	Slice 3	0-1	0-1	0-1	0-1
	Slice 4	0-1	0-1	0-1	0-1
	Slice 5	0-1	0-1	0-1	0-1
	Slice 6	0-1	0-1	0-1	0-1
	Total score	0-6	0-6	0-6	0-6
	Total score per SI-joint	0-12		0-12	
	Total score (both SI-joints)	0-24			

* Since ankylosis always involves a sacral and an iliac part, it will always be scored in two quadrants.
SI-joint, sacroiliac joint.

Supplementary Table 2: Scenario 1: *Addition* of MRI-SI-s to the ASAS axSpA-criteria (≥ 3 erosions only) reader 1/*reader 2*

		ASAS axSpA classification criteria								
		Negative	Only clinical arm positive	Only MRI active positive	Only mNY positive	Clinical arm and MRI active positive	Clinical arm and mNY positive	Clinical arm, MRI active positive, mNY positive	Both MRI active and mNY positive	**Total**
ASAS axSpA-criteria: **addition of MRI-SI-s**	Negative	163/*152*								**160/*157***
	Only clinical arm positive	0	175/*160*							**169/*162***
	Only MRI active positive	0	0	46/*37*						**42/*34***
	Only MRI-SI-s/mNY positive	1/*12*	0	0	13/*13*					**16/*19***
	Clinical arm and MRI active positive	0	0	0	0	61/*43*				**57/*41***
	Clinical arm and MRI-SI-s/mNY positive	0	1/*16*	0	0	0	19/*19*			**26/*33***
	Clinical arm, MRI active and MRI-SI-s/mNY positive	0	0	0	0	4/*22*	0	77/*77*		**85/*101***
	MRI active and MRI-SI-s/mNY positive	0	0	4/*13*	0	0	0	0	18/*18*	**26/*34***
	Total	**164/*164***	**176/*176***	**50/*50***	**13/*13***	**65/*65***	**19/*19***	**77/*77***	**18/*18***	**582/*582***

Classification remains the same

mNY- patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY- patients not fulfilling the ASAS axSpA-criteria, became ASAS axSpA positive based on MRI-SI-s+

Not possible in this scenario

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

Supplementary Table 3: Scenario 2: *Replacing mNY-criteria* by MRI-SI-s in the ASAS axSpA classification (≥ 3 erosions only) reader 1/*reader 2*

	ASAS axSpA classification criteria	Negative	Only clinical arm positive	Only MRI active positive	Only mNY positive	Clinical arm and MRI positive	Clinical arm and mNY positive	Clinical arm, MRI active positive, mNY positive	Both MRI active and mNY positive	**Total**
ASAS axSpA-criteria: **replacement of X-SI by MRI-SI-s**	Negative	163/*152*	0	0	13/*10*	0	0	0	0	**176/*162***
	Only clinical arm positive	0	175/*160*	0	0	0	17/*10*	0	0	**192/*170***
	Only MRI active positive	0	0	46/*37*	0	0	0	0	17/*10*	**63/*47***
	Only MRI-SI-s positive	1/*12*	0	0	0/*3*	0	0	0	0	**1/*15***
	Clinical arm and MRI active positive	0	0	0	0	61/*43*	0	58/*29*	0	**119/*72***
	Clinical arm and MRI-SI-s positive	0	1/16	0	0	0	2/*9*	0	0	**3/*25***
	Clinical arm, MRI active and MRI-SI-s positive	0	0	0	0	4/*22*	0	19/*48*	0	**23/*70***
	MRI active and MRI-SI-s positive	0	0	4/*13*	0	0	0	0	1/*8*	**5/*21***
	Total	**164/*164***	**176/*176***	**50/*50***	**13/*13***	**65/*65***	**19/*19***	**77/*77***	**18/*18***	**582/*582***

Classification remains the same

mNY- patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY- patients not fulfilling the ASAS axSpA-criteria, became ASAS axSpA positive based on MRI-SI-s+

mNY+ patients became MRI-SI-s-, but remained classified ASAS axSpA positive

mNY+ patients became ASAS axSpA-criteria negative because of MRI-SI-s-

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

Supplementary Table 4: Scenario 1: *Addition* of MRI-SI-s to the ASAS axSpA-criteria (≥ 3 fatty lesions only) reader 1/*reader 2*

		ASAS axSpA classification criteria								
		Negative	Only clinical arm positive	Only MRI active positive	Only mNY positive	Clinical arm and MRI active positive	Clinical arm and mNY positive	Clinical arm, MRI active positive, mNY positive	Both MRI active and mNY positive	**Total**
ASAS axSpA-criteria: **addition of MRI-SI-s**	Negative	160/*158*								**160/*158***
	Only clinical arm positive	0	166/*162*							**166/*162***
	Only MRI active positive	0	0	39/*41*						**39/*41***
	Only MRI-SI-s/mNY positive	4/*6*	0	0	13/*13*					**17/*19***
	Clinical arm and MRI active positive	0	0	0	0	56/47				**56/*47***
	Clinical arm and MRI-SI-s/mNY positive	0	10/*14*	0	0	0	19/*19*			**29/*33***
	Clinical arm, MRI active and MRI-SI-s/mNY positive	0	0	0	0	9/*18*	0	77/*77*		**86/*95***
	MRI active and MRI-SI-s/mNY positive	0	0	11/*9*	0	0	0	0	18/*18*	**29/*27***
	Total	**164/*164***	**176/*176***	**50/*50***	**13/*13***	**65/*65***	**19/*19***	**77/*77***	**18/*18***	**582/*582***

Classification remains the same

mNY- patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY- patients not fulfilling the ASAS axSpA-criteria, became ASAS axSpA positive based on MRI-SI-s+

Not possible in this scenario

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

Supplementary Table 5: Scenario 2: *Replacing mNY-criteria* by MRI-SI-s in the ASAS axSpA classification (≥ 3 fatty lesions only) reader 1/*reader 2*

		ASAS axSpA classification criteria								
		Negative	Only clinical arm positive	Only MRI active positive	Only mNY positive	Clinical arm and MRI positive	Clinical arm and mNY positive	Clinical arm, MRI active positive, mNY positive	Both MRI active and mNY positive	**Total**
ASAS axSpA-criteria: **replacement of X-SI by MRI-SI-s**	Negative	160/*158*	0	0	12/*10*	0	0	0	0	**172/*168***
	Only clinical arm positive	0	166/*162*	0	0	0	7/*12*	0	0	**173/*174***
	Only MRI active positive	0	0	39/*41*	0	0	0	0	11/*10*	**50/*53***
	Only MRI-SI-s positive	4/*6*	0	0	1/*3*	0	0	0	0	**5/*9***
	Clinical arm and MRI active positive	0	0	0	0	56/*47*	0	44/*34*	0	**100/*81***
	Clinical arm and MRI-SI-s positive	0	10/*14*	0	0	0	12/*7*	0	0	**22/*21***
	Clinical arm, MRI active and MRI-SI-s positive	0	0	0	0	9/*18*	0	33/*43*	0	**42/*61***
	MRI active and MRI-SI-s positive	0	0	11/*9*	0	0	0	0	7/*8*	**18/*17***
	Total	**164/*164***	**176/*176***	**50/*50***	**13/*13***	**65/*65***	**19/*19***	**77/77**	**18/*18***	**582/*582***

Classification remains the same

mNY- patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY- patients not fulfilling the ASAS axSpA-criteria, became ASAS axSpA positive based on MRI-SI-s+

mNY+ patients became MRI-SI-s-, but remained classified ASAS axSpA positive

mNY+ patients became ASAS axSpA-criteria negative because of MRI-SI-s-

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

7

Impact of replacing radiographic sacroiliitis by magnetic resonance imaging structural lesions on the classification of patients with axial spondyloarthritis

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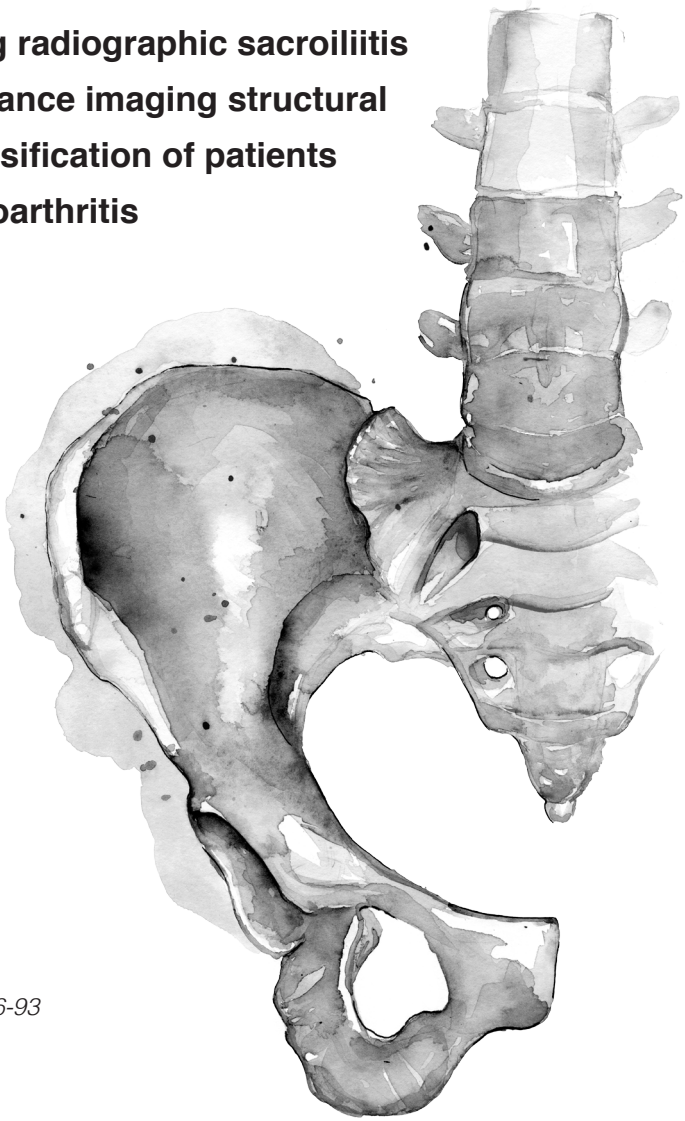

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ABSTRACT

Objectives

To investigate in patients with chronic back pain of a short duration, the utility of adding structural MRI lesions of the SI joints to the imaging criterion of the Assessment of SpondyloArthritis International Society (ASAS) axial SpA (axSpA) criteria and the utility of replacement of radiographic sacroiliitis by structural MRI lesions.

Methods

MRI STIR (inflammation, MRI-SI), MRI T1-weighted images (structural lesions, MRI-SI-s) and radiographs of the SI joints of patients in the SPondyloArthritis Caught Early-cohort (chronic back pain: ≥3 months, ≤2 years; onset <45 years) were scored by two well-calibrated readers. Previously proposed cut-offs for a positive MRI-SI-s were used (based on <5% prevalence in no-SpA patients): erosions ≥3, fatty lesions ≥3, fatty lesions and/or erosions (erosions/fatty lesions) ≥5. Using the definitions of MRI-SI-s, patients were classified according to the ASAS axSpA criteria.

Results

Twenty-nine of 294 patients were modified New York (mNY) positive and 32 were MRI-SI-s positive (erosions/fatty lesions ≥5). Agreement between mNY and MRI-SI-s (erosions/fatty lesions ≥5) was moderate (k: 0.58). Using the erosions/fatty lesions ≥5 cut-off, 3/294 additional patients were classified as axSpA (adding MRI). Using this cut-off instead of mNY (replacing mNY), classification did not change in 286 patients (97.3%), but 5 patients (1.7%) would not be classified as axSpA and 3 previously unclassified patients (1.0%) would be classified as axSpA. Similar results were seen for the other cut-offs (erosions ≥3 and fatty lesions ≥3).

Conclusion

Assessment of structural lesions (fatty lesions and erosions) on MRI-SI instead of or in addition to conventional radiographs does not lead to a different ASAS axSpA classification in most of the patients with early disease onset. This suggests that structural lesions (fatty lesions and erosions) can be reliably used in the ASAS axSpA classification of patients, as both addition and replacement of radiographs of the SI joints.

INTRODUCTION

Recently, we have demonstrated that in the DEvenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort of patients with inflammatory back pain with a high suspicion of having axial SpA (axSpA), structural lesions on MRI can be used reliably either as an addition to or as a substitute for radiographs in the Assessment of SpondyloArthritis International Society (ASAS) axSpA classification of patients with spondyloarthritis.[1] Since this is a new concept with potential consequences for daily clinical practice, replication in other cohorts is highly warranted. The current study investigates the same research question in an entirely independent cohort, the SPondyloArthritis Caught Early (SPACE) cohort of patients with chronic back pain of a short duration.

The rationale behind using structural lesions on MRI instead of conventional radiographs is mainly based on the fact that a reliable detection of sacroiliitis on conventional radiographs is notoriously difficult. Sacroiliitis is the hallmark of AS and the presence of sacroiliitis on conventional radiography is obligatory in the modified New York (mNY) criteria for AS.[2] However, it has been shown that substantial observer variation (interreader, intrareader) exists for both radiologists and rheumatologists, and training does not lead to improvement.[2] Recent data from the DESIR cohort have also revealed a poor to moderate agreement between different readers leading to substantial misclassification of patients.[3] With the help of MRI it has become possible to detect active sacroiliitis (bone marrow oedema, BME) in early stages of axSpA. The ASAS definition for a positive MRI is solely based on identification of BME highly suggestive for SpA, but structural lesions can be seen [fatty lesions, erosions, sclerosis and (partial) ankylosis] are visible on MRI as well.[4] The 3D (albeit tomographic) character of MRI may be an advantage as compared with the 2D projection of conventional radiographs.[5] Another advantage of MRI above radiography is that patients are not exposed to ionizing radiation.

Both the SPACE and the DESIR are cohorts of early disease. Since it often takes 6-8 years from the onset of symptoms before radiographic sacroiliitis can be detected on plain radiographs, conventional radiography is a suboptimal imaging technique especially in patients with complaints of a short duration (in addition to the earlier described reliability issues). The DESIR cohort only includes patients with inflammatory back pain (IBP) with up to 3 years of symptoms, whereas the SPACE cohort includes patients with chronic back pain (CBP) with up to 2 years of symptoms. Different reader pairs were involved in the scoring process of the two cohorts, to rule out a reader-dependent effect.

In this study we aim to evaluate the usefulness of structural lesions with regard to the ASAS axSpA classification criteria in the SPACE cohort. First of all, we determine the agreement between sacroiliitis seen on radiographs (mNY) and structural lesions seen on MRI. Then we aim to evaluate the potential impact of adding structural lesions on MRI to the definition of a positive MRI or replacing radiographic sacroiliitis by MRI structural lesions on the ASAS axSpA classification of patients.

METHODS

Study population

For this analysis, baseline data from the SPACE cohort were used. An extensive description of the SPACE cohort has been given elsewhere.[6] In short, SPACE is an inception cohort with on-going inclusion and follow-up of patients with CBP of short duration (≥3 months but ≤2 years, with onset <45 years). Patients were recruited from five participating centres in the Netherlands (Leiden, Amsterdam, Gouda), Norway (Oslo) and Italy (Padua). Approval by the local medical ethics committees was obtained, as well as written informed consent from all patients in accordance with the Declaration of Helsinki.

A full diagnostic work-up was performed in all patients including: HLA-B27 testing, conventional radiographs and MRI of the SI joints (X-SI and MRI-SI, respectively), and the assessment of all other SpA features, in agreement with the descriptions supplied by the ASAS group.[7]

Imaging and scoring methods

MRI-SI was performed on a 1.5 Tesla machine (Philips Medical Systems, Best, Netherlands). Coronal oblique T1-weighted TSE (TR 550/TE 10) and STIR (TR 2500/TE 60) with a slice thickness of 4 mm were the acquired sequences used. All available baseline MRI-SI and X-SI were read independently, in different reading sessions, by two trained, well-calibrated readers (P.A.B., M.d.H.). Readers were blinded to the score of the other reader and other modality as well as the clinical information, throughout the scoring process.

The mNY criteria were used to assess radiographs of the SI joints; radiographic sacroiliitis was defined as bilateral grade 52 or unilateral grade 53.[8] In consensus with the ASAS definition, an MRI-SI was defined positive if one BME lesion highly suggestive of SpA was present on two or more consecutive slices, or otherwise if several BME lesions highly suggestive of SpA were visible on a single slice.[9] A third reader served as adjudicator (R.vd.B.) in case of disagreement among the two initial readers regarding a positive MRI (ASAS definition) or the presence of sacroiliitis (mNY criteria).

The presence of structural lesions, namely fatty lesions, erosions, sclerosis and (partial) ankylosis, was assessed on MRI T1-weighted images in conjunction with the STIR images. A scoring system with similarities to the methodology outlined in the Spondyloarthritis Research Consortium of Canada (SPARCC) online training module, as described by Weber et al. was used.[10] Weber et al. proposed a scoring system to quantify structural lesions called SPARCC SI structural lesion score. This method is founded on the assessment of lesions (present vs absent) counting them in each quadrant on six consecutive slices through the SI joints. The starting point is the slice on which at least 1 cm of vertical height of the cartilage compartment can be seen, from anterior to posterior evaluating the cartilaginous compartment of the SI joints and the antero-inferior portion of the SI joint. Each SI joint is split into four quadrants. Structural lesions were taken into account only if present on at least two consecutive slices. This is reflected by a maximum score of 40 per lesion (5 lesions per quadrant 4 quadrants 2 SI joints) except for (partial) ankylosis. As an exception, (partial) ankylosis was considered sufficient when seen on a single slice reflected by a maximum score of 24 per patient.

As shown earlier by our group, an MRI positive for structural lesions (MRI-SI-s) was determined by the use of different cut-offs.[11] These chosen cut-offs were anchored on 45% false positives whereby the false positives were specified as structural lesions among patients not having axSpA according to the ASAS axSpA criteria. The described cut-offs have pointed out to be: erosions ≥3, fatty lesions ≥3, fatty lesions and/or erosions ≥5. In this early cohort, the prevalence of sclerosis and (partial) ankylosis was so low that there was no cut-off that could clearly differentiate between SpA and no-SpA patients. As a consequence, these types of lesions were not further considered.

Classification criteria

Patients were classified according to the ASAS axSpA criteria. Subsequently, patients were grouped based on the way they met the criteria: through the imaging arm of the ASAS axSpA criteria alone (either by mNY criteria and/or by positive MRI); through the clinical arm of the ASAS axSpA criteria alone; or through both. If patients fulfilled more than one category, they were classified in that way, reflected by seven possible combinations (Table 3 and 4). The no-axSpA group is made up of patients not fulfilling the ASAS axSpA criteria.

Data analysis

Descriptive statistics were used to calculate disease characteristics of the included patients. In the analysis, regarding structural lesions the mean score of the two readers in agreement of a positive MRI (ASAS definition) was used. In case of disagreement, the mean of the scores of the adjudicator and the reader in agreement with the adjudicator's judgement regarding a positive MRI for that particular case were used.

Agreement about the absence or presence of structural lesions using both imaging modalities (X-SI and MRI-SI-s) was assessed by cross-tabulation and expressed as Cohen's k. Percentage positive agreement was calculated in order to leave out patients labelled as negative by the two readers, which could lead to an artificially high agreement.

Subsequently, using the various definitions of MRI-SI-s, patients were classified by the ASAS axSpA criteria. MRI-SI-s was added to the imaging criterion of the ASAS axSpA criteria in the first place, resulting in an additional possibility to fulfil the imaging arm (scenario 1). Second, replacement of the mNY criterion by MRI-SI-s (scenario 2) was applied as if only an MRI was performed.

Disease probabilities were calculated by the positive likelihood ratio (LR) product, for those patients changing ASAS axSpA classification in scenario 2. This was done by multiplying the individual LRs of all identified SpA features.[12] In patients with CBP with an assumed disease prevalence of axSpA of 5%, an LR product of 200 results in a positive predictive value of 90%. These patients were further described by their clinical phenotype: gender, age and whether a patient was diagnosed as axSpA according to the treating rheumatologist. The analyses were performed in STATA 12.0 (StataCorp LP, College Station, Texas, USA).

RESULTS

Included in the analysis are 294 patients with complete imaging data at baseline (both MRI-SI and X-SI present). Table 1 describes patient characteristics. Patients had a mean (S.D.) age of 31.6 years of age (10.7 years) and a mean (S.D.) duration of back pain of 13.1 months (7.3 months). Of these patients, 34.6% were men and 34.6% were HLA-B27 positive.

One hundred and three out of 294 patients (35.0%) fulfilled the ASAS axSpA criteria using the standard definition. Of these 103 patients, 50 patients fulfilled the imaging arm (48.5%) and 53 patients fulfilled the clinical arm only (51.5%). The most prevalent SpA features were IBP (62.6%), a positive family history for SpA (38.1%) and a good response to NSAIDs (31.6%).

Regarding the prevalence of structural lesions, 20/294 patients (6.8%) showed three or more fatty lesions; 16 of these 20 patients (80%) already formally fulfilled the ASAS axSpA criteria. Thirty-four patients (11.6%) had three or more erosions, and 27 of these 34 (79.4%) already formally fulfilled the ASAS axSpA criteria. Thirty-one patients (10.5%) had 5 or more fatty and/or erosive lesions (combination), of which 26 patients (83.9%) already formally fulfilled the ASAS axSpA criteria.

Table 1: Baseline characteristics of the SPACE cohort

	Total number (n=294)
Age at inclusion, mean (SD), years	31.6 (10.7)
Male, n (%)	102 (34.6)
Symptom duration at first visit, mean (SD), months	13.1 (7.3)
Good response to NSAIDs, n (%)	92 (31.6)
IBP, n (%)	184 (62.6)
Positive family history SpA, n (%)	112 (38.1)
Peripheral arthritis, n (%)	37 (12.6)
Dactylitis, n (%)	10 (3.4)
Enthesitis, n (%)	43 (14.6)
Uveitis, n (%)	21 (7.1)
IBD, n (%)	26 (8.8)
Psoriasis, n (%)	29 (9.7)
Elevated CRP, n (%)	54 (18.8)
HLA-B27 positive, n (%)	100 (34.6)
Sacroiliitis present on radiograph, n (%)	29 (9.8)
Positive MRI (ASAS definition), n (%)	37 (12.5)

SPACE, Spondyloarthritis Caught Early; NSAIDs, non-steroidal anti-inflammatory drugs; IBP, inflammatory back pain; SpA, spondyloarthritis; IBD, inflammatory bowel disease; CRP: C-reactive protein; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; ASAS, Assessment of SpondyloArthritis international Society.

Table 2: Agreement between sacroiliitis on conventional radiographs (mNY criteria) and a positive MRI-SI based on structural lesions (MRI-SI-s)

		mNY (adjudicated)		**κ: 0.51**
		Positive	Negative	Total
Erosions: cut-off ≥3; mean 2 out of 3 readers	Positive	18	17	35
	Negative	11	248	259
	Total	29	265	294
		mNY (adjudicated)		**κ: 0.45**
		Positive	Negative	Total
Fatty lesions: cut-off ≥3; mean 2 out of 3 readers	Positive	12	8	20
	Negative	17	257	274
	Total	29	265	294
		mNY (adjudicated)		**κ: 0.58**
		Positive	Negative	Total
Erosions/fatty lesions: cut-off ≥5; mean 2 out of 3 readers	Positive	19	13	32
	Negative	10	252	262
	Total	29	265	294

Agreement based on MRI-SI structural lesions (MRI-SI-s) using the three different definitions.
mNY, modified New York criteria; MRI-SI-s, MRI of the sacroiliac joints assessed for structural lesions.

The agreement regarding the presence/absence of radiographic sacroiliitis and the presence/absence of structural lesions on MRI was moderate (Table 2). Subtle differences were seen between the various definitions used: k: 0.51 (erosions ≥3); k: 0.45 (fatty lesions ≥3); and k: 0.58 (combination of fatty lesions and erosions ≥5).

Scenario 1

The addition of MRI-SI-s to the imaging criterion of the ASAS axSpA criteria was investigated first (Table 3). Classification did not change in the majority of the patients (96.3%) using a cut-off value of 5 for the combination of fatty lesions and/or erosions. If a cut-off value of 3 for erosions or fatty lesions only was used, comparable results were seen: classification did not change in 94.9 and 97.6% of the patients, respectively. Considering the combination of five fatty lesions and/or erosions, three patients would be classified additionally axSpA if structural lesions on MRI were taken into consideration. The positive LR products of the three additionally classified patients were 15.8, 5.1 and 2.5, corresponding to post-test probabilities of 44, 20 and 11%, respectively. The rheumatologist diagnosed only one of these three patients (all female and HLA-B27 negative) with axSpA. Regarding the definition based on erosions, five patients would be additionally classified (all female and HLA-B27 negative). Only two of them were diagnosed as axSpA by the rheumatologist. Regarding the definition based on fatty lesions, three patients would be additionally classified as axSpA (one was described above, the other two were male patients, HLA-B27 negative, of whom one was diagnosed as having axSpA by the rheumatologist).

Some patients changed subgroups within the ASAS classification, without a change in ASAS axSpA positivity or negativity. Eight patients would be classified via different arms due to the presence of structural lesions, using the combination of fatty lesions and/or erosions. Five patients also showed structural lesions on MRI (Table 3) but were already classified via the imaging arm based on inflammatory lesions on MRI. Three other patients fulfilled the clinical arm only, but fulfilled the imaging arm as well based on a positive MRI-SI-s. Using the cut-offs for fatty lesions or erosions only (both cut-off values were 3), the same trends were seen (data not shown).

Scenario 2

Second, the replacement of radiographic sacroiliitis by structural lesions on MRI (Table 4) and its impact on the ASAS axSpA classification was assessed. Using the same cut-off values of 5 for the combination of fatty lesions and/or erosions, classification did not change in the large majority of the patients (93.5%). A similar result was seen at a cut-off value of 3 for erosions and fatty lesions only: classification did not change in 91.8 and 92.9% of the patients, respectively. The same patients would be additionally classified as axSpA as in scenario 1. But assuming that only an MRI was performed, five patients (1.7%) would not be classified axSpA anymore if radiographic sacroiliitis was replaced by structural lesions on MRI using the combination of fatty lesions and/or erosions. The SpA-features of the patients that are newly classified by the ASAS axSpA criteria are described in Table 5, and the SpA-features of the patients that are no longer classified by the ASAS axSpA criteria are described in Table 6.

Table 3: Scenario 1: *Addition* of MRI-SI-s to the ASAS axSpA-criteria (combination fat and/or erosions)

		ASAS axSpA classification criteria								
		Negative	Only clinical arm positive	Only MRI active positive	Only mNY positive	Clinical arm and MRI positive	Clinical arm and mNY positive	Clinical arm, MRI active positive, mNY positive	Both MRI active and mNY positive	**Total**
ASAS axSpA classification criteria: **addition of MRI-SI-s**	Negative	188								**188**
	Only clinical arm positive	0	50							**50**
	Only MRI active positive	0	0	10						**10**
	Only MRI-SI-s/mNY positive	3	0	0	8					**11**
	Clinical arm and MRI active positive	0	0	0	0	9				**9**
	Clinical arm and MRI-SI-s/mNY positive	0	3	0	0	0	7			**10**
	Clinical arm, MRI active and MRI-SI-s/mNY positive	0	0	0	0	3	0	7		**10**
	MRI active and MRI-SI-s/mNY positive	0	0	2	0	0	0	0	4	**6**
	Total	**191**	**53**	**12**	**8**	**12**	**7**	**7**	**4**	**294**

Classification remains the same

mNY- patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY- patients became ASAS axSpA positive due to MRI-SI-s+

Not possible in this scenario

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

Table 4: Scenario 2: *Replacing mNY-criteria* by MRI-SI-s in the ASAS axSpA classification

		ASAS axSpA classification criteria								
		Negative	Only clinical arm positive	Only MRI active positive	Only mNY positive	Clinical arm and MRI positive	Clinical arm and mNY positive	Clinical arm, MRI active positive, mNY positive	Both MRI active and mNY positive	**Total**
ASAS axSpA classification criteria: **replacement of X-SI by MRI-SI-s**	Negative	188	0	0	5	0	0	0	0	**193**
	Only clinical arm positive	0	50	0	0	0	1	0	0	**51**
	Only MRI active positive	0	0	10	0	0	0	0	0	**10**
	Only MRI-SI-s positive	3	0	0	3	0	0	0	0	**6**
	Clinical arm and MRI active positive	0	0	0	0	9	0	2	0	**11**
	Clinical arm and MRI-SI-s positive	0	3	0	0	0	6	0	0	**9**
	Clinical arm, MRI active and MRI-SI-s positive	0	0	0	0	3	0	5	0	**8**
	MRI active and MRI-SI-s positive	0	0	2	0	0	0	0	4	**6**
	Total	**191**	**53**	**12**	**8**	**12**	**7**	**7**	**4**	**294**

Classification remains the same

mNY- patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY+ patients became MRI-SI-s+ within ASAS axSpA positive classification

mNY- patients became ASAS axSpA positive due to MRI-SI-s+

mNY+ patients became ASAS axSpA criteria negative because of MRI-SI-s-

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; mNY, modified New York; MRI-SI, magnetic resonance imaging of the sacroiliac joints; MRI-SI-s, MRI-SI assessed for structural lesions.

Table 5: ASAS axSpA negative patients becoming ASAS axSpA positive (due to MRI-SI-s positive) scenario 2 (the patients marked in purple in Table 4)

Gender	Age	Diagnosis SpA yes/no	IBP	NSAIDs good reaction	Peripheral arthritis	Raised CRP/ESR	Enthesitis	IBD	Positive family history	Uveitis	Dactylitis	Psoriasis	HLA-B27+	Pos. MRI acc. ASAS	mNY-criteria	Probability of axSpA*
Female	32.5	No	0	1	0	0	0	0	0	0	0	0	0	0	0	21%
Female	44.2	Yes	0	0	0	1	0	0	0	0	0	0	0	0	0	11%
Female	28.7	No	1	1	0	0	0	0	0	0	0	0	0	0	0	44%

Patients that changed in cut-offs: combination fatty lesions/erosions ≥5

SpA-feature positive

**Probability of axSpA is based on the LR+ product. [reference 12]*

SpA, spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory Drugs; IBP, inflammatory back pain; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; ASAS, Assessment of SpondyloArthritis international Society; mNY, modified New York, axSpA, axial spondyloarthritis.

Table 6: ASAS axSpA positive patients (mNY+) becoming ASAS axSpA negative (due to MRI-SI-s negative) in scenario 2 (the patients marked in blue in Table 4)

Gender	Age	Diagnosis SpA yes/no	IBP	NSAIDs good reaction	Peripheral arthritis	Raised CRP/ESR	Enthesitis	IBD	Positive family history	Uveitis	Dactylitis	Psoriasis	HLA-B27+	Pos. MRI acc. ASAS	mNY-criteria	Probability of axSpA*
Female	37.6	Yes	1	0	0	1	1	0	0	1	0	0	0	0	1	91%
Male	20.5	Yes	0	0	0	0	0	0	1	0	0	0	1	0	1	75%
Male	20.6	No	0	1	0	0	0	0	0	0	0	0	0	0	1	21%
Female	37.4	Yes	1	0	0	0	0	0	0	0	0	0	0	0	1	14%
Female	17.1	No	0	0	0	0	0	0	0	0	0	0	1	0	1	32%

Patients that changed in cut-offs: combination fatty lesions/erosions ≥5

SpA-feature positive

**Probability of axSpA is based on the LR+ product. [reference 12]*

SpA, spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory Drugs; IBP, inflammatory back pain; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; ASAS, Assessment of SpondyloArthritis international Society; mNY, modified New York, axSpA, axial spondyloarthritis.

One of these patients had four axSpA features, leading to a positive LR product of 192.4 and a corresponding high disease probability of 91%. One other patient had a disease probability of 75%. The disease probabilities of the other three patients turned out to be much lower: between 14 and 32%. Three of these five patients were female and two of the five patients were HLA-B27 positive (one male, one female). Of the five patients who would not be classified as axSpA anymore in this scenario, three patients were diagnosed axSpA by the rheumatologist. Regarding the definition based on erosions only, one additional patient would not be classified as ASAS axSpA anymore. This female patient was HLA-B27 negative, and was not diagnosed axSpA by the treating rheumatologist. Regarding the combination of fatty lesions and/or erosions, 11 patients changed arms within the criteria under this scenario but all stayed ASAS axSpA positive. Similar results were found when using a cut-off for fatty lesions only and erosions only (both cut-off values of 3) (data not shown).

DISCUSSION

In this cohort of patients with CBP of short duration we have shown that adding structural lesions to the imaging criterion of the ASAS axSpA criteria has a limited effect on the classification of patients. Also, when sacroiliitis on radiographs was replaced by structural lesions on MRI, only minor changes in the ASAS axSpA classification of patients were seen. In patients with CBP suspicious for axSpA, structural lesions are associated with other SpA features and the majority of patients with structural lesions in our study fulfil the ASAS axSpA criteria anyway.

If conventional radiographs were replaced by MRI-SI-s, using a combination of fatty lesions and erosions, only 3/294 (1.0%) patients would be additionally classified as ASAS axSpA. On the other hand, only 5/294 (1.7%) patients would lose their ASAS axSpA classification. Three out of these five patients with a state change had relatively low ratio products and corresponding probabilities of axSpA, suggesting that they did not have classic disease presentations. However, the two other patients have high disease probabilities and therefore could be missed erroneously. Most changes that are seen are a change in a subcategory between the various ASAS axSpA criteria rather than a change in classification per se. In other words, patients do not lose their ASAS classification solely by changing the content of the criteria. This characteristic adds to the credibility of the ASAS criteria.

Only a few patients lose ASAS axSpA classification in scenario 2, which may justify replacement of conventional radiographs by MRI. However, it is important to realize that this is purely data-driven and feasibility issues should not be overlooked. MRI is an expensive imaging technique, especially in certain areas of the world. Furthermore, rheumatologists and radiologists are worldwide familiar with the mNY criteria, and evaluation of structural lesions

on an MRI of the SI joints is a new concept. Education and time is needed in order to become familiarized with it. At this point in time, we therefore favour the addition of structural lesions to the imaging criterion of the ASAS axSpA criteria above replacement.

These results are in line with recent data from the DESIR cohort, investigating the same research question in another cohort. In the SPACE cohort, even more patients do not change classification while replacing radiographic sacroiliitis by structural lesions seen on MRI compared with DESIR (SPACE: 95.3% vs DESIR: 80%). In general, a notable difference between the two cohorts is that in DESIR only patients with IBP are included, whereas in SPACE 62.6% of the patients have IBP. Other SpA features are also more common in the DESIR cohort, among which HLA-B27 positivity and radiographic sacroiliitis on conventional radiography and inflammation on MRI are highlighted. This is reflected in the fact that in the DESIR cohort, 71.8% fulfil the ASAS axSpA classification criteria, compared with 35.0% in the SPACE cohort. In DESIR all patients included are of French origin, whereas the SPACE cohort recruits patients from three European countries (The Netherlands, Italy, Norway). Though there might not be a big disparity between the prevalence of axSpA and CBP in general between these countries, it is important to observe these results in two populations of a different origin.

Reliability of structural lesions remains a difficult issue and in a research setting often two or more well-calibrated readers are involved, which may cause difficulties translating this to clinical practice. So we should also be informed on the agreement between evaluation of MRI-SI-s in clinical practice before this can be advocated for use in a clinical setting. A limitation of the study is the absence of a gold standard to assess structural changes in the SI joint, by means of CT.

Although the agreement regarding the presence/absence of radiographic sacroiliitis and the presence/absence of structural lesions on MRI in this study is only moderate, it is slightly better compared with the similar study in the DESIR cohort.[1] In general, it is reassuring to see consistent findings in two independent cohorts with different (though well-trained) reader pairs. This increases confidence regarding the generalizability.

Although the research question has now been investigated in two cohorts, both cohorts include patients with short-standing back pain complaints and it would be very interesting to see replication of these findings in cohorts with advanced disease before possible far-reaching conclusions can be drawn on potentially changing ASAS axSpA classification criteria. The ideal cut-off could potentially be different in patients with longer symptom duration and more structural lesions in the SI joints. In general, more data are warranted on the prevalence of structural lesions in advanced disease, and it is beyond the scope of this study how lesions develop over time.

Although the focus of this study is the impact of structural lesions on the ASAS axSpA classification criteria, we could speculate about possible implications for the diagnostic process. The modified Berlin algorithm advises that all patients suspected of axSpA should have a plain radiograph of the pelvis to check for sacroiliitis as a first step.[13] In patients without evidence of radiological sacroiliitis in whom axSpA still is suspected, an MRI of the SI joints (assessed for inflammation only) may support a diagnosis of non-radiographic axial spondyloarthritis when inflammation is present. Our data suggest that there is no solid indication to change the strategy of first asking a pelvic radiograph, since the classification remains very similar when replacing pelvic X-rays by MRI-s. However, in young patients MRI can be obtained as an alternative to plain radiography. This is in line with the recently published EULAR recommendations.[14] Similarly, if an MRI (STIR and T1 sequence) is present in a clinical setting, but there is no pelvic radiograph, this MRI may suffice and there is no reason to obtain radiographs.

A strength of the study is the intensive scoring process by two well-calibrated readers with an adjudication process in place, which adds to the reliability of our findings. Another strength of this study is the SPACE cohort itself. The SPACE cohort is one of early disease, and comprises a control group of (chronic) back pain patients, just as in daily practice where a distinction between axSpA and no-axSpA should be made in every patient presenting with a suspicion of axSpA.

In conclusion, our study has confirmed the earlier promising finding that the assessment of structural lesions on MRI instead of or in addition to conventional radiographs does not lead to a different ASAS axSpA classification in most of these patients with symptoms of an early disease onset.

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8

Is it useful to repeat MRI of the sacroiliac joints after three months or one year in the diagnostic process of patients with chronic back pain suspected of axial spondyloarthritis?

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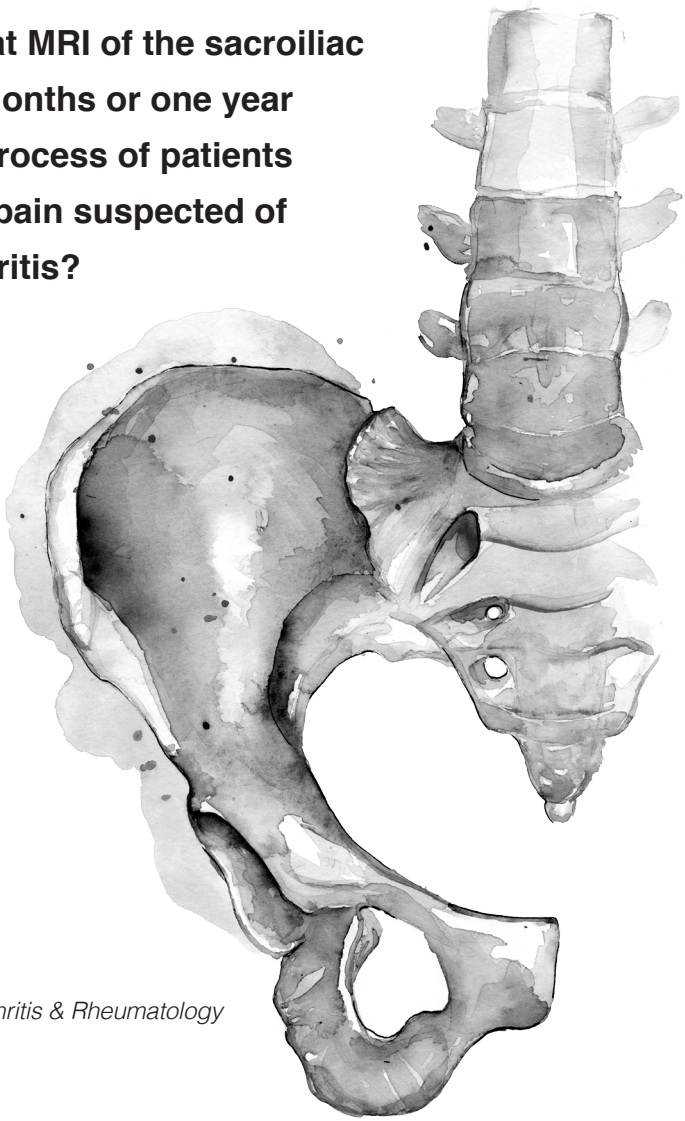

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ABSTRACT

Objective

To investigate the value of repeating MRI of the sacroiliac joints (MRI-SI) in the diagnostic process of early chronic back pain patients (CBP) suspected of axial SpondyloArthritis (axSpA) and study determinants of MRI-SI-positivity.

Methods

Patients with CBP (duration: ≥3 months, ≤2 year, onset <45 years) with ≥1 SpA-feature included in the SPondyloArthritis Caught Early cohort underwent baseline, three months and one year visits with evaluation of all SpA-features and repeated MRI-SI. MRI-SI-positivity according to ASAS was assessed by two (or three) well-trained readers, blinded for clinical information. Factors determining MRI-SI-positivity over follow-up were calculated by GEE analysis.

Results

Of the 188 patients (38.3% male, mean (SD) age 31.0 (8.2) years, symptom duration 13.2 (7.1) months), 31 (16.5%) were MRI-SI-positive at baseline. After three months and one year 3/27 (11.1%) and 11/29 (37.9%) patients changed from MRI-SI positive to negative, respectively which was partly induced by the start of anti-TNF therapy. Changes from negative to positive were seen in 5/116 (4.3%) and 10/138 (7.2%) patients, respectively. HLA-B27-positivity and male gender independently determined the likelihood of a positive MRI at any time point (42% in HLA-B27+ men and 6% in HLA-B27- females). If the baseline MRI is negative, the likelihood of a positive MRI during follow-up is very low (max 7%).

Conclusions

MRI-SI ASAS status changes are seen in a minority of the patients. Both male gender and HLA-B27-positivity are important predictors of MRI-positivity. Repeating MRI after three months or one year in the diagnostic work-up in early disease is not useful.

INTRODUCTION

In the diagnostic process of axial spondyloarthritis (axSpA), sacroiliac joint imaging plays a pivotal role.[1] Conventional radiography has always been and still is the most commonly used method to detect sacroiliitis. However, it is known that radiographic abnormalities evolve over several years of time, which contributes to a reported delay of 8-9 years in diagnosis.[2,3] This substantial delay in diagnosis is problematic since effective treatments are available for patients with axSpA.[4-6] Over the last decade, Magnetic Resonance Imaging (MRI) rapidly gained ground and proved to be an important imaging technique in the diagnostic process of (non-radiographic) axial spondyloarthritis.[7] It has been shown that MRI can detect the early inflammatory stages of sacroiliitis, months to years before structural damage can be detected on a conventional radiograph.[8,9] Besides the fact that MRI has substantial advantages in terms of sensitivity, MRI has the benefit of providing information on activity and structural damage by one imaging modality.[10-12]

Axial spondyloarthritis (axSpA) should be considered in patients with chronic back pain (CBP) with an onset before 45 years of age. Regrettably, no formal diagnostic criteria exist and there is no single SpA-feature with sufficient specificity to establish the diagnosis. The modified Berlin algorithm is a helpful tool for rheumatologists in establishing an early diagnosis of axSpA with greater confidence.[1] According to this algorithm, MRI of the sacroiliac joints (MRI-SI) should be performed in a certain group of patients after obtaining conventional radiographs and HLA-B27 testing.[13] The more recently published EULAR recommendations on imaging in SpA even state that in certain cases, such as young patients and those with short symptom duration, MRI of the SI-joints is an alternative *first* imaging method.[14]

Although inflammation on MRI is now widely considered as an important manifestation in early axSpA, not much evidence is available on how inflammatory lesions develop over time (outside clinical trials).[15,16] Though, with the augmented interest of MRI in the early diagnosis of axSpA this is important. We do know that inflammatory lesions (bone marrow edema, BME) can change over relatively short periods of time in patients diagnosed with SpA. But in patients with CBP and with a suspicion of axSpA, it is unclear if BME-lesions newly develop or fluctuate over time. For example, a relevant clinical question is if an MRI is completely normal and there is still a clinical suspicion of axSpA, should the MRI be repeated? And if so, after what period of follow-up? Or does this not contribute to the diagnostic process? The SPondyloArthritis Caught Early (SPACE) cohort is an ideal cohort to investigate this research question since it includes a population of patients with back pain of short duration referred to rheumatologists with a suspicion of SpA (but without the mandatory presence of a single or multiple SpA-features). With this study, we aim to investigate the evolution of MRI-lesions over a 3-month and 1-year time frame in the SPACE-cohort.

METHODS

Study design and patient population

SPACE is a multi-national ongoing cohort study, started in January 2009. Across five participating centres in Europe, patients with chronic back pain (≥3 months, ≤2 years, onset <45 years; aged 16 years and older) are included. Before start of the study, approval was obtained by the local medical ethics committees. Before inclusion, written informed consent was obtained from all patients in accordance with the Declaration of Helsinki. A detailed description of the SPACE cohort has been given elsewhere.[17] All patients underwent a diagnostic work-up at baseline. This includes a physical examination, MRI and radiographs of the SI-joints (MRI-SI, X-SI respectively), HLA-B27 testing and examination of all other SpA-features.[13,18] Patients fulfilling the Assessment of SpondyloArthritis international Society (ASAS) axSpA-criteria at baseline or patients with possible axSpA (i.e. the presence of SpA-features though not sufficient to be classified as axSpA, defined as the presence of ≥1 SpA-feature) were included for follow-up visits. At three months and 1-year follow-up, clinical and laboratory data were again collected and another MRI-SI was performed. It was considered arbitrarily that three month MRI data of about 150 patients was sufficient to answer the question about the change over three months and therefore decided to leave out the three month MRI in the patients included in the cohort after July 2012.

Imaging and scoring methodology

MRI-SIs were performed on a 1.5 Tesla MRI-scanner at baseline and follow-up. Coronal oblique MRI images were obtained, with a slice thickness of 4 millimetres. Both short tau inversion recovery (STIR) and T1 weighted turbo spin echo (T1TSE) sequences were acquired and evaluated in the scoring process. At baseline, conventional radiographs of the pelvis (sacroiliac joints) in anterior-posterior view (X-SI) were performed. MRI-SIs and X-SIs were scored independently by two trained and well-calibrated readers, blinded for patient characteristics, clinical data, time sequence and the other imaging modality. In case of discrepancy on dichotomous scores a third reader scored the images (see below for details).

A radiograph was marked positive for sacroiliitis according to the fulfilment of the modified New York (mNY) criteria: at least bilateral grade 2 sacroiliitis or at least unilateral grade 3 sacroiliitis was mandatory.[19] According to the ASAS definition for a positive MRI, an MRI-SI was marked positive if ≥1 bone marrow edema (BME) lesion highly suggestive of SpA was present on ≥2 consecutive slices or if several BME lesions highly suggestive of SpA are visible on a single slice.[7,18] MRIs were also scored according to the SPondyloArthritis Research Consortium of Canada (SPARCC) score which measures inflammation on a continuous

scale (range: 0-72).[20] According to the SPARCC score, the presence of increased signal corresponding to BME lesions is marked on 6 consecutive slices of an MRI-SI. The maximum score for two SI-joints on each slice is 8. In addition to these 8 points per slice, a score for intensity (adding 1 point) may be assigned to each SI-joint if a so-called intense signal is seen in any quadrant on each slice. The signal from pre-sacral blood vessels defined a lesion that is scored as intense. Further, a score for depth (adding 1 point) may be assigned to each SI-joint if a homogeneous and unequivocal increase in signal is extending over a depth of at least 1 cm from the articular surface on each slice, resulting in a maximum score of 12 points per slice. For assessment of both the ASAS definition and the SPARCC score on the STIR sequence, the readers took into account the findings on the T1TSE sequences, looking at both sequences simultaneously.

In case of disagreement on the presence of radiographic sacroiliitis (mNY) or a positive MRI (ASAS-definition) amongst the two initial readers, a third reader served as adjudicator (final score: two out of three agreeing readers). The SPARCC scores of the two agreeing readers on a positive MRI were used for further analysis.

Statistical methods

Disease characteristics of patients were presented using descriptive statistics. Then, we described the MRI-SI ASAS-status over time in different ways. First, by depicting the course of MRI-SI ASAS status at the (two or three) available time points and second, by means of a two-by-tow table reflecting changes in MRI ASAS-status (positive-negative). Agreement on the absence or presence of MRI-SI ASAS inflammation was assessed by cross-tabulation and expressed as Cohen's kappa. Cumulative probability plots were used to visualize baseline and 1 year-SPARCC-scores in which patients were grouped according to either positivity or negativity according to the ASAS-definition. Subsequently, patients of special interest, i.e. in which the MRI changed from positive to negative or vice versa after three months and one-year follow-up, were described phenotypically: according to the presence of SpA-features and other disease characteristics. Thereafter, we investigated the likelihood of having a positive MRI at any time point during follow-up and identified which factors determine MRI-SI ASAS-positivity. After the analysis for the whole group of patients, we repeated this analysis in the subset of patients that have IBP according to the ASAS definition. Subsequently, we looked at the likelihood of having a positive MRI in the follow-up time points (3 months or 1 year), taking into account the baseline MRI (positive vs negative), first in all patients and secondly in the subgroup of patients with IBP. This was done by using generalised estimated equation (GEE) analysis for binomial outcome variables: MRI ASAS status was defined as the dependent variable, HLA-B27 and gender being independent explanatory variables. CRP was added to the model as a covariate, in order to assess the contribution of CRP

in explaining a positive MRI. The likelihood of finding a positive MRI if the baseline MRI is either positive or negative was calculated, taking into account HLA-B27 status and gender. Odds ratios from the model were converted into probabilities (likelihood).[21] Data analysis was performed using Stata SE v. 14 software (StataCorp LP, College Station), TX, USA).

RESULTS

Patient characteristics

In total, 188 patients were included in the current study. Baseline characteristics were described in Table 1. The mean age of the included patients was 31.0 years (SD 8.2 years) and 38.3% were male. The mean symptom duration of back pain was 13.2 months (SD 7.1 months) and 139 patients (74.3%) had inflammatory back pain according to the ASAS criteria definition. Almost half of the patients (48.4 %) were HLA-B27 positive.

Table 1: Baseline characteristics

	Total number (n=188)
Age (years) at inclusion, mean (SD)	31.0 (8.2)
Male, n (%)	72 (38.3%)
Symptom duration (months) at first visit, mean (SD)	13.2 (7.1)
Good response to NSAIDs, n (%)	76 (41.3%)
IBP, n (%)	139 (74.3%)
Positive family history SpA, n (%)	96 (51.3%)
Peripheral arthritis, n (%)	34 (18.2%)
Dactylitis, n (%)	15 (8.0%)
Enthesitis, n (%)	41 (21.9%)
Uveitis, n (%)	16 (8.6%)
IBD, n (%)	17 (9.1%)
Psoriasis, n (%)	25 (13.4%)
Elevated CRP, n (%)	35 (18.9%)
HLA-B27 positive, n (%)	91 (48.4%)
Sacroiliitis present on radiograph, n (%)	19 (11.1%)
Positive MRI (ASAS definition), n (%)	31 (16.5%)
Diagnosis axSpA according to rheumatologist, n (%)*	74 (39.6%)

ASAS, Assessment of SpondyloArthritis; axSpA, axial spondyloarthritis; CRP, C-reactive protein; HLA-B27, human leukocyte antigen-B27; IBD, inflammatory bowel disease; IBP, inflammatory back pain; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs.
*Confidence level ≥7 (NRS 0-10).

MRI findings

Agreement between the two readers regarding the definition of a positive MRI-SI according to the ASAS definition was good: kappa 0.85. In 8 of the 188 cases (4.3%) adjudication was needed since reader 1 and reader 2 were in disagreement on the MRI-SI ASAS status.

The course of MRI-SI ASAS positivity over time is visualised in Table 2. In 122 out of 188 patients, all three time points were available: baseline, three months and one-year follow-up. In 66 out of 188 patients, MRI was performed at two time points: in 21/66 patients at baseline and three months' follow-up and in 45/66 patients at baseline and one-year follow-up. In all three scenarios mentioned above, the vast majority of patients 77.1% (145/188) had a negative MRI according to the ASAS definition at baseline which did not change at the follow-up time point(s) (triple/double-negative). In patients with all three time points available, persistence of a positive MRI was seen in (15/122) 12.3% of the patients (triple-positive) and (21/122) 17.2% of the patients showed MRI fluctuations over time (for instance: 0-0-1; 1-1-0; 0-1-1 etcetera).

Table 2: Course of MRI-SI ASAS positivity over one-year time

	MRI-SI ASAS definition over time	Number of patients
Patients with MRI-SI available at baseline & 3 months & 1 year (a)	0-0-0	86
	1-1-1	15
	0-0-1	7
	1-1-0	7
	0-1-1	3
	1-0-0	2
	1-0-1	1
	0-1-0	1
	Total	**122**
Patients with MRI-SI available at baseline & 3 months (b)	0-0	18
	1-1	2
	0-1	1
	Total	**21**
Patients with MRI-SI available at baseline & 1 year (c)	0-0	41
	1-1	2
	1-0	2
	Total	**45**

*0=MRI ASAS negative; 1 = MRI ASAS positive; cases with all three time points available (a), cases with baseline & 3 months available (b) and cases with 3 months & 1 year available (c).
MRI-SI, magnetic resonance imaging of the sacroiliac joints; ASAS, Assessment of SpondyloArthritis international Society.

Changes in MRI-SI ASAS-status over time are depicted in another way by means of a two-by-two table (Table 3). In contrast to Table 2, data are clustered, shown independently of the availability of the third time point. The upper part of the table reflects changes over three months and changes over one-year time are shown in the lower part of the table. In 8 out of 143 patients (5.6%) a change in MRI-SI ASAS status was seen after three months' follow-up. After a year follow-up, the percentage with a change in MRI-SI status was slightly higher: 12.6% (21/167). The MRI of 10 of 138 patients (7.2%) turned from negative to positive after one year follow-up (compared to 5/116 (4.3%) patients after three months) and on the other hand, 11 out of 29 (37.9%) patients with a positive MRI-SI ASAS at baseline were negative after one year of follow-up (compared to 3/27 (11.1%) patients after three months). Thus, relatively more patients become negative in comparison to patients that develop a positive MRI. To visualise the amount of BME, cumulative probability plots for each of the readers, of baseline and 1 year-SPARCC-scores in which patients were grouped according to either positivity or negativity according to the ASAS-definition are given in Supplementary Figure 1a and b.

Table 3: Changes in MRI-SI ASAS positivity over three months and one-year time

	MRI 3 months ASAS positive	MRI 3 months ASAS negative	Total
MRI baseline positive	24	3	27
MRI baseline negative	5	111	116
Total	**29**	**114**	**143**

	MRI 1 year ASAS positive	MRI 1 year ASAS negative	Total
MRI baseline positive	18	11	29
MRI baseline negative	10	128	138
Total	**28**	**139**	**167**

MRI, magnetic resonance imaging; ASAS, Assessment of SpondyloArthritis international Society.

With special interest, we reviewed the patients with a change in MRI-SI-ASAS status; their disease characteristics are depicted in Table 4. Three of the five patients that turned ASAS MRI-positive after three months (Table 4, orange cells) were male (60%) and three patients (60%) were HLA-B27 positive. One patient had sacroiliitis on radiographs (mNY-criteria) at baseline. After three months, two patients developed a new SpA-feature, namely good response on NSAIDs. One patient used NSAIDs on baseline, whilst three (60%) after three months. All three patients with an initial positive MRI according to the ASAS definition that turned negative (Table 4, blue cells) were on NSAID treatment from baseline, were men and HLA-B27 positive.

Table 4: Disease characteristics of patients with a change in MRI-SI-ASAS status over 3 months and 1 year

	mNY+	HLA-B27	Age	Sex+	SpA-features*		CRP		ASDAS		Medication		SPARCC score reader 1 - reader 2	
					Baseline	3 months	Baseline	3 months	Baseline	3 months	Baseline	3 months	Baseline	3 months
1	1	Positive	19	M	1, 2	Idem	3	5	0.8	-	-	-	0/0	5/6
2	0	Negative	38	F	1, 3	Idem	3	5	-	-	NSAID	NSAID	1/1	2/2
3	0	Positive	25	M	2, 8	Idem + 9	6	4	1.6	-	-	NSAID	0/0	10/7
4	0	Negative	29	F	1	Idem	3	1	0.9	-	-	-	0/0	9/12
5	0	Positive	26	M	1, 2	Idem + 9	3	3	1.6	-	-	NSAID	0/0	5/5
6	1	Positive	21	M	1, 9	Idem	6	14	1.4	-	NSAD	NSAID	3/5	0/3
7	0	Positive	32	M	1, 6, 9	Idem	3	4	3.8	-	NSAID	NSAID	2/4	0/0
8	0	Positive	31	M	1, 6, 8, 9	Idem	9	2	3.4	-	NSAID	NSAID	2/2	0/0
	mNY+	**HLA-B27**	**Age**	**Sex+**	**SpA-features***		**CRP**		**ASDAS**		**Medication**		**SPARCC score** reader 1 – reader 2	
					Baseline	1 year	Baseline	1 year	Baseline	1 year	Baseline	1 year	Baseline	1 year
9	0	Positive	21	F	1, 2, 5, 9	Idem	3	3	2.2	2.9	NSAID	NSAID	0/0	4/3
10	1	Positive	33	M	1, 4	Idem + 9	3	3	0.9	2.3	-	NSAID	0/0	5/6
11	1	Positive	19	M	1, 2	Idem	3	1	0.8	0.4	-	NSAID	0/0	16/18
12	0	Positive	31	M	1,2	Idem	3	3	2.4	2.4	NSAID	NSAID	0/2	2/3
13	0	Positive	32	M	1	Idem	13	9	3.0	3.2	NSAID	NSAID	0/0	3/2
14	0	Positive	19	F	2	Idem	4	1	3.3	1.2	NSAID	NSAID	0/0	2/2
15	0	Negative	32	F	1, 2, 6, 9	Idem	1	1	2.7	-	NSAID	NSAID	1/0	5/5
16	0	Positive	25	M	2, 8	Idem + 1, 7, 9	6	3	1.6	-	-	NSAID	0/0	10/7
17	1	Positive	35	F	9	Idem	3	10	2.5	-	-	NSAID	1/0	14/11
18	0	Negative	29	F	1	Idem	3	1	0.9	1.0	-	NSAID	0/0	13/16
19	0	Negative	43	F	1, 6	Idem + 5	1	1	1.4	1.1	-	-	3/2	0/0
20	1	Positive	29	F	1	Idem + 9	1	1	1.6	1.4	NSAID	NSAID +anti-TNF	14/14	0/0
21	0	Positive	31	M	1, 6, 8, 9	Idem + 7	9	1	3.4	0.8	NSAID	NSAID	2/2	0/0
22	0	Negative	40	F	1	Idem + 4, 9	4	4	2.1	3.7	-	Anti-TNF	8/8	0/0
23	1	Positive	22	M	-	1, 2, 9	3	3	3.1	2.7	NSAID	NSAID	9/13	1/0
24	0	Positive	32	M	1, 6, 9	Idem + 2	3	3	3.8	-	NSAID	NSAID	2/4	0/0
25	0	Positive	33	M	1, 8, 9	Idem	23	1	2.9	1.0	NSAID	Anti-TNF	7/5	0/0
26	0	Negative	46	M	1, 9	Idem	4	4	2.7	1.6	NSAID	NSAID	4/2	1/0
27	1	Positive	24	F	2, 5, 6	Idem + 1, 9	3	3	3.0	1.0	NSAID	NSAID +anti-TNF	46/44	0/0
28	1	Positive	42	M	6, 9	Idem	1	1	3.0	1.0	NSAID	NSAID	10/9	0/0
29	1	Positive	26	M	1, 2	Idem	2	2	2.0	2.3	-	NSAID	18/16	2/0

* 1=IBP; 2=positive family history; 3=uveitis; 4=IBD; 5=psoriasis; 6=enthesitis; 7=dactylitis; 8=peripheral arthritis; 9=NSAID response.
+ mNY status and age at baseline.
Orange cells: reflect patients in which a negative MRI-SI at baseline turned positive after 3 months follow-up.
Blue cells: reflect patients in which a positive MRI-SI at baseline turned negative after 3 months follow-up.
Green cells: reflect patients in which a negative MRI-SI at baseline turned positive after 1 year follow-up.
Red cells: reflect patients in which a positive MRI-SI at baseline turned negative after 1 year follow-up.
mNY, modified New York-criteria; SpA-feature, spondyloarthritis feature; CRP, C-reactive protein; ASDAS, Ankylosing Spondylitis Disease Activity Score; SPARCC-score, scoring system developed by the SPondyloArthritis Research Consortium of Canada; NSAID, non-steroidal anti-inflammatory drug; anti-TNF, Tumour Necrosis Factor alpha antagonists; IBP, inflammatory back pain; IBD, inflammatory bowel disease.

Of the 10 newly MRI-SI positive patients at one-year follow-up (Table 4, green cells) 5 patients were male (50%) and the majority (n=8, 80%) was HLA-B27 positive. Sacroiliitis on radiographs (mNY criteria at baseline) was present in 30% of the patients (3/10). Two patients developed new SpA-feature(s) over one-year time, which were not yet present at baseline (patient 10: good response on NSAIDs, patient 16: good response on NSAIDs, inflammatory back pain and dactylitis). All 10 patients used NSAIDs after one-year follow-up (50% at baseline) and there were no patients on anti-TNF treatment in this group. Of the 11 patients that started with a positive baseline MRI, which became negative at one year (Table 4, red cells), the majority was male (n=7, 64%) and HLA-B27 (n=8, 73%) and developed new SpA features (n=6, 55%). Four patients had started anti-TNF therapy and one patient started an NSAID.

SPARCC scores are depicted in the last column of Table 4. Overall, when comparing SPARCC scores between the two different readers, only modest differences are seen, which implies a high level of agreement. Reviewing patients becoming newly ASAS positive (after three months or one year: Table 4, orange and green cells), half of the patients become marginally positive in terms of SPARCC scores whilst other patients become evidently positive with a marked raise in SPARCC scores up to 18. After one year, patients that were initially ASAS positive but became negative over time (Table 4, red cells) had mostly low SPARCC scores except those that have been treated (patients were treated according to clinical practice). Four patients were on anti-TNF therapy which showed an important decrease in SPARCC-scores at one-year follow-up.

Factors determining a positive MRI

According to the GEE analysis, both HLA-B27 positivity (OR: 2.36, 95% CI: 1.09-5.12, p=0.029) and male gender (OR: 5.63, 95% CI: 2.58-12.27, p<0.001) independently determined the likelihood of a positive MRI at any time point.

Figure 1 displays the effects of HLA-B27 and sex in an absolute manner. The likelihood of a positive MRI in HLA-B27 negative women with CBP is only 7%, whereas in HLA-B27 positive men this is 43.0% (HLA-B27 positive women: 6%, HLA-B27 negative men: 14%). In men, HLA-B27 positivity or -negativity has a significant effect on the likelihood of having a positive MRI at any time point (OR: 4.54, 95% CI: 1.50-13.79, p=0.008) whereas this effect was not present in women (OR: 0.84, 95% CI: 0.23-3.12, p=0.800). Influences of CRP were investigated in all models, but correcting for CRP had only very minor influence. Therefore, data uncorrected for CRP are shown. Only minor differences were seen between patients with CBP and IBP according to the ASAS definition (data not shown).

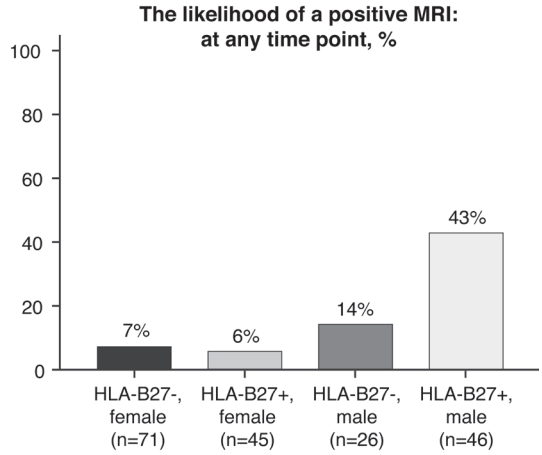

Figure 1: Likelihood of a positive MRI at any time point in CBP patients investigated at baseline, 3 months and 1-year follow-up in the subgroups of patients according to HLA-B27 status and gender
HLA-B27, human leukocyte antigen B27.

Likelihood of a positive MRI during follow-up

The likelihood of finding a positive MRI at 3 months or 1 year according to the baseline MRI status (either positive or negative) was considered. Both HLA-B27 status (OR: 2.41, 95% CI: 0.94-6.18, p=0.067) and MRI baseline status (OR: 43.89, 95% CI: 17.59-109.52, p<0.001) were independently contributory to a positive MRI at follow-up. This analysis was repeated with sex instead of HLA-B27 status: both sex (OR: 2.54, 95% CI: 1.01-6.39, p=0.048) and MRI baseline status (OR: 36.04, 95% CI: 14.42-90.08, p<0.001) appeared to be independently contributory to a positive MRI over time. Again, only minor changes were seen between CBP and IBP patients, not reaching significance (data not shown).

In Figure 2, the likelihood of a positive MRI in relation to baseline MRI and HLA-B27 status (a) and sex (b) is visualized. In an HLA-B27 negative patient with a negative baseline MRI, the likelihood of a positive MRI at follow-up is negligible (1.5%). On the contrary, in an HLA-B27 positive patient with a positive baseline MRI-SI, the likelihood is rather high: 73%. In patients with a positive MRI on baseline, HLA-B27 status does not influence the likelihood of a positive MRI at any follow-up time point (OR: 0.65, 95% CI: 0.14-2.96, p=0.582). However, in MRI baseline negative patients, HLA-B27 positivity or negativity has a significant effect on the likelihood of a positive MRI at follow-up (OR: 8.12, 95% CI: 1.65-40.11, p=0.010).

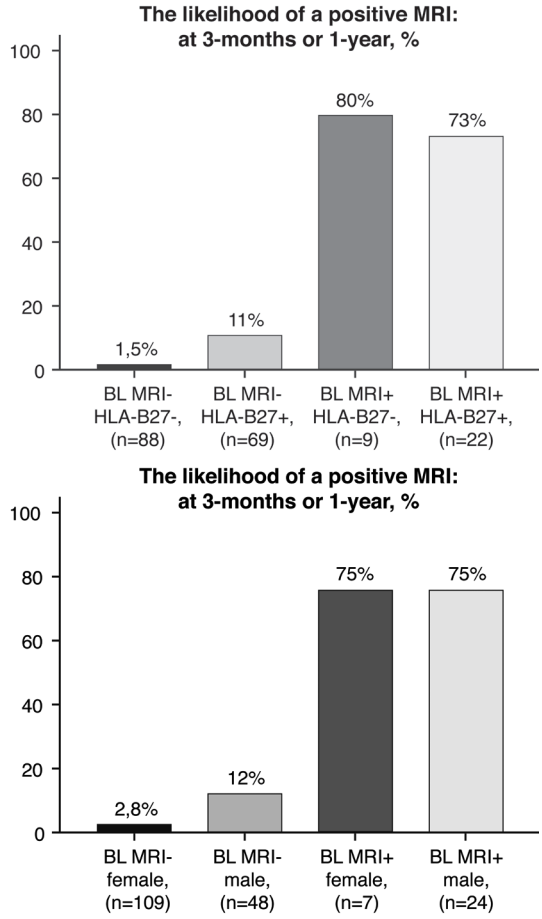

Figure 2: Likelihood of a positive MRI at three months or 1-year follow-up in CBP patients, in the subgroups of patients according to the result of the baseline MRI (negative or positive) and HLA-B27 status (a) or sex (b)
HLA-B27, human leukocyte antigen B27; BL, baseline.

For sex, in a male or female patient with a positive baseline MRI the likelihood of having a positive MRI at 3 months or 1 year follow-up is 75%, whereas it is only 2.8% in a female patient with a negative baseline MRI and 12% in a male patient with a negative MRI at baseline. In patients with a negative baseline MRI, there is a significant effect of sex (OR: 4.67, 95% CI: 1.41-15.44, p=0.01) while this is absent in patients with a positive MRI on baseline (OR: 0.96, 95% CI: 0.20-4.54, p=0.959).

As an example, MRI-SIs of patients with an ASAS status change over 1 year time are depicted in Supplementary Figure 2: two patients being MRI-SI ASAS positive at baseline, but negative after 1 year (a) and two patients being MRI-SI ASAS negative at baseline, but positive after 1 year (b).

DISCUSSION

In this study of patients with chronic back pain suspicious for axial SpA, 83.5% of the patients (157/188) had a negative MRI at baseline. Of these patients, only (12/157) 7.6 % had a positive MRI at any follow-up time point. Twelve of the 31 patients (38.7%) with a positive MRI at baseline had a negative MRI at any follow-up time point. Although changes are visible in both directions, relatively more patients become negative (4.3% after three months and 7.2% after one year) than positive (11.1% after 3 months and 37.9% after one year). Nevertheless, it is important to realise that 36% of the patients that became negative after one year started anti-TNF therapy, which is known to decrease inflammation in the sacroiliac joints visible on MRI.[16]

This study showed that MRI status at baseline appeared to be strongly influencing the chance of having a positive MRI of the sacroiliac joints at follow-up. If the baseline MRI is positive, the likelihood that the MRI will be positive again at three months or one year is very high (75%). The usefulness of repeating a negative MRI in terms of diagnostic yield is low, but there are different risks related to sex and HLA-B27 status.

In baseline MRI negative patients, HLA-B27 status has a significant effect on the likelihood of a positive MRI at follow-up. In HLA-B27 negative patients with a negative MRI at baseline, sacroiliitis at follow-up can be excluded with a high level of confidence. The likelihood of a positive MRI at follow-up is only 1.5%. In HLA-B27 positive patients with a negative MRI at baseline, the likelihood of a positive MRI at three months or one year is still low, though somewhat higher (namely 11%). Of course, we can debate on the clinical relevance of this small difference in terms of percentage and, in general, chances of MRI positivity at follow-up are very low when the baseline MRI is negative. But, if a clinical suspicion about the diagnosis axial spondyloarthritis remains (for example a patient develops other SpA features) it might be worthwhile to consider re-doing an MRI in HLA-B27 positive patients. Likewise, there is a statistically significant difference between male and female patients with a negative baseline MRI, namely that in male patients more often a positive MRI at follow-up is seen (difference: 12% in men, 3% in women). Of course, interpretation of MRI findings should always be determined in the context of all clinical, laboratory and other imaging parameters available, for example other SpA-features that enhance diagnostic confidence. Also, other findings on MRI (for example the presence of structural lesions) can be supportive in the diagnostic process. However, in this group of patients with short symptom duration, the frequency of structural changes in SI-joints is relatively low and only discriminates between patients with and without axial SpA if at least 5 structural lesions (especially erosions and fatty lesions) are present.[11] This indicates that at this phase of the disease, BME is the most important feature.

Van Onna et al. performed a two-year follow-up study, which observed MRI status changes in 15% of the patients with recent-onset inflammatory back pain (IBP) that can be seen as relatively similar to our data, although follow-up time is considerably shorter in our study.[22] On the other hand, in our study substantially more patients are included and two validated scoring methods are used. Like in our study, in the study by van Onna et al. relatively more patients became negative in comparison to patients that developed a positive MRI over time: 30% became negative (while positive at baseline) and 15% became positive (while negative at baseline) at one or two years follow-up. They also found that male gender and HLA-B27 positivity were predictive of a positive MRI-SI at follow up. In our study too, male gender and HLA-B27 positivity determined independently the likelihood of a positive MRI at any time point. HLA-B27 positive male patients with chronic back pain, have the highest chance of a positive MRI at any time. Other studies have investigated the natural history of MRI-determined BME in individuals with suspected axSpA as well. Sengupta et al. concluded that in patients fulfilling the ASAS IBP criteria repeat MRI scans within a 12-week period should only be considered in HLA-B27 positive males; since there were no HLA-B27-negative patients changed from MRI-negative to –positive in this study. Although this was a considerably smaller group of patients, data are in line with our findings that HLA-B27 positivity determines the likelihood of a positive MRI.[23] Marzo-Ortega et al. also reported a higher chance of a positive MRI at one year in early, untreated IBP patients being HLA-B27 positive.[24]

Regarding sex differences, historically ankylosing spondylitis (AS) was considered as a predominantly male disease, but it has been reported that 46% of the patients diagnosed since 1990 were female compared to 10% in 1960.[25] This suggests that the male predominance in AS and axSpA may be (at least in part) induced by missing the diagnosis of AS among women in earlier times and more data become available that the percentage female patients with non-radiographic axial SpA and AS is substantial. Another reason for the higher male/female ratio in AS may be that men develop more often radiographic sacroiliitis compared to females. This is also in line with our findings that male patients are more likely to have a positive MRI at any time point, as a positive MRI is a predictor of development of radiographic sacroiliitis.[9]

Another issue is timing: when to re-do an MRI in case of persistent axSpA suspicion and after what period of follow-up. With this study, we looked at both three months and one-year follow-up, and at both time points the additional value is very limited. Given the low diagnostic yield, taking costs and feasibility into account, repeating an MRI after 3 months or 1 year should not be performed routinely. Two-year data on the SPACE cohort will become available in the future, which will provide information on a longer interval.

In general, MRI has become an important tool in the evaluation of patients with axSpA and relevant improvements in the field have taken place: such as the standardization of imaging protocols, and the development and validation of standardized descriptions of lesions. These lesions include not only inflammatory lesions, but also structural lesions: by means of fatty lesions, erosions, sclerosis and ankylosis. MRI has the unique potential of visualizing both inflammatory and structural lesions by means of one imaging technique and it is hypothesized that structural lesions could enhance sensitivity and/or specificity which could be helpful when in diagnostic doubts. Research on the incremental value of structural lesions is ongoing.

Looking at methodological aspects, the fact that we have repeated MRI in all patients irrespective of the diagnosis is an important strength of our study compared to studies doing this in a selected population of patients. Moreover, the follow-up is quite complete avoiding unintentional bias in leaving out patients with a low likelihood of axial SpA. Another strength of our study is our scoring process with two readers with adjudication in case of discrepancy, which adds to the credibility of the findings. Moreover, the fact that we used two well-validated scoring methods (ASAS and SPARCC) provides additional insight. On the other hand, limitations of the current study are the limited duration of follow-up and the fact that we could not compare these findings with an external standard. Diagnosis is influenced by MRI findings and would lead to circular reasoning. Moreover, we lack another imaging technique like low-dose CT or histology. Prospective evaluation over a sufficient time frame with a longer follow-up should enhance confidence in the diagnosis of this sometimes slowly evolving disease.

In conclusion, MRI-SI ASAS status changes are seen in a minority of the patients of the SPACE cohort and both changes from negative to positive and from positive to negative occur. Especially a very small percentage of patients become positive (4.3% and 7.2% after three months and one year, respectively), which indicates that the usefulness of repeating an MRI-SI in the diagnostic process after three months or one year is very limited. Relatively more patients become negative (37.9% after one year) and one should realize that resolution of inflammation is partly induced by the use of anti-TNF therapy. Male gender and HLA-B27 positivity determine independently the likelihood of a positive MRI at any time point, while MRI-SI status at baseline strongly predicts MRI-SI status at follow-up.

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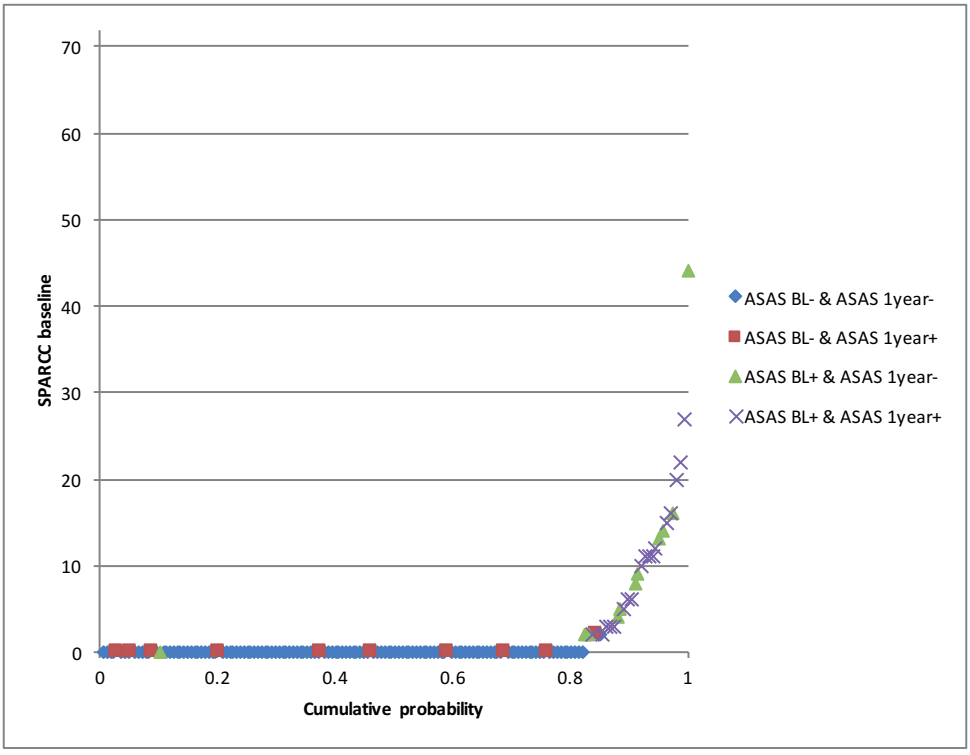
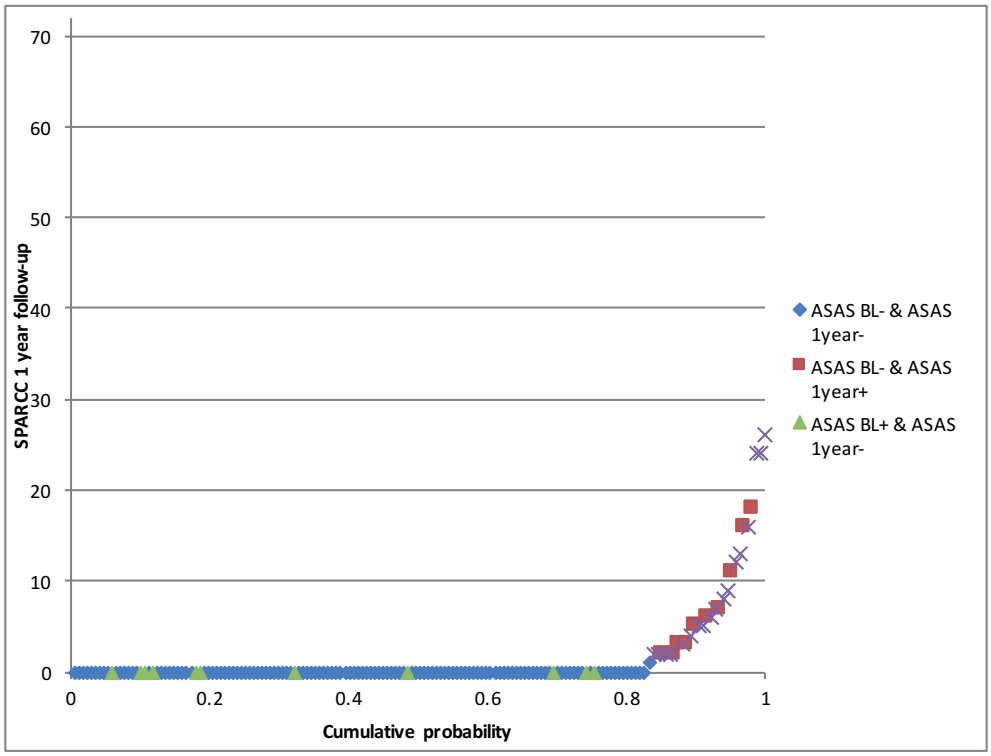
SUPPLEMENTARY MATERIAL



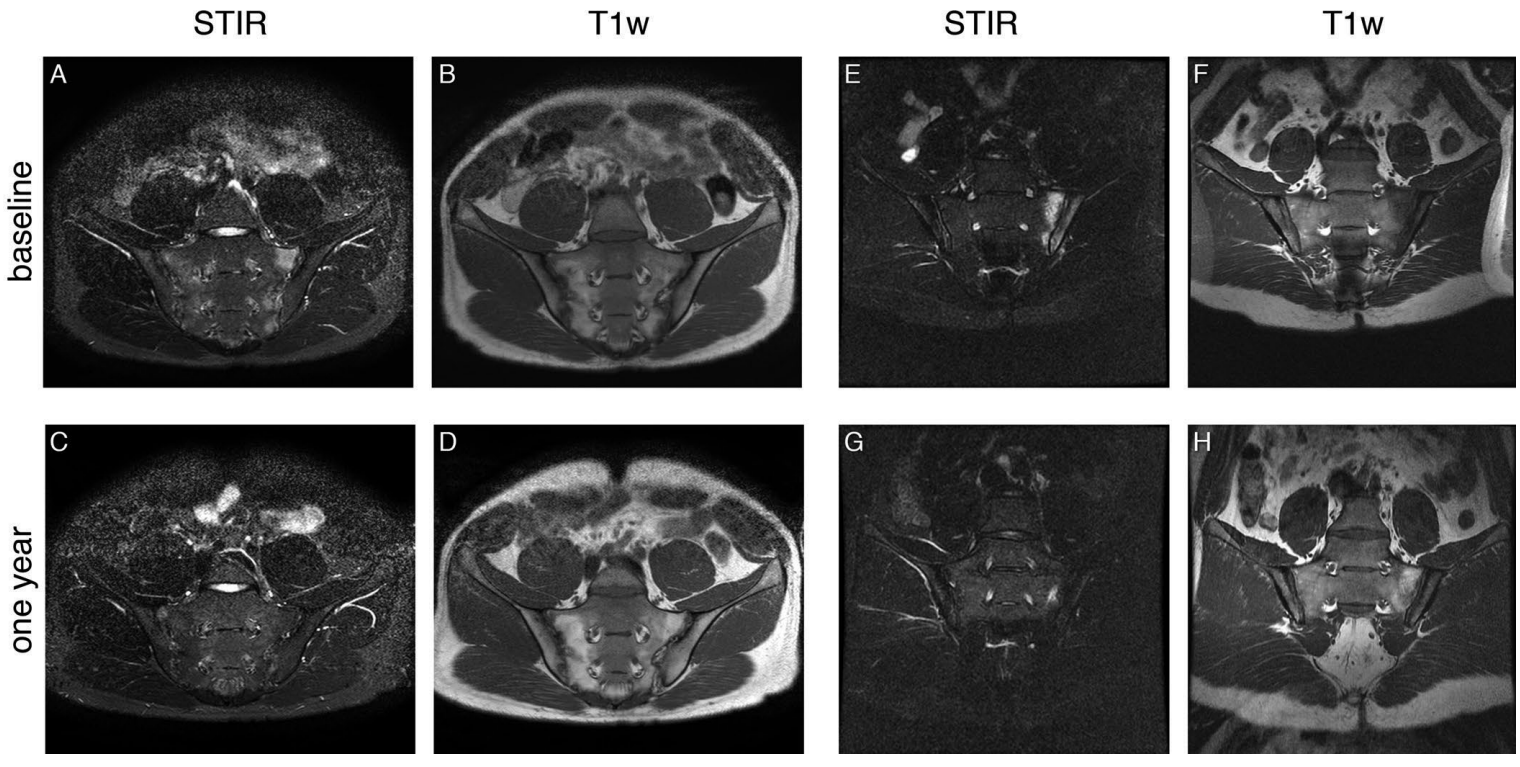
Supplementary Figure 1a: Cumulative probability plot of baseline and 1 year-SPARCC-scores in which patients were grouped according to either positivity or negativity according to the ASAS-definition – *reader 1*

ASAS, Assessment of SpondyloArthritis; axSpA, axial spondyloarthritis; BL, baseline; SPARCC, SPondyloArthritis Research Consortium of Canada.



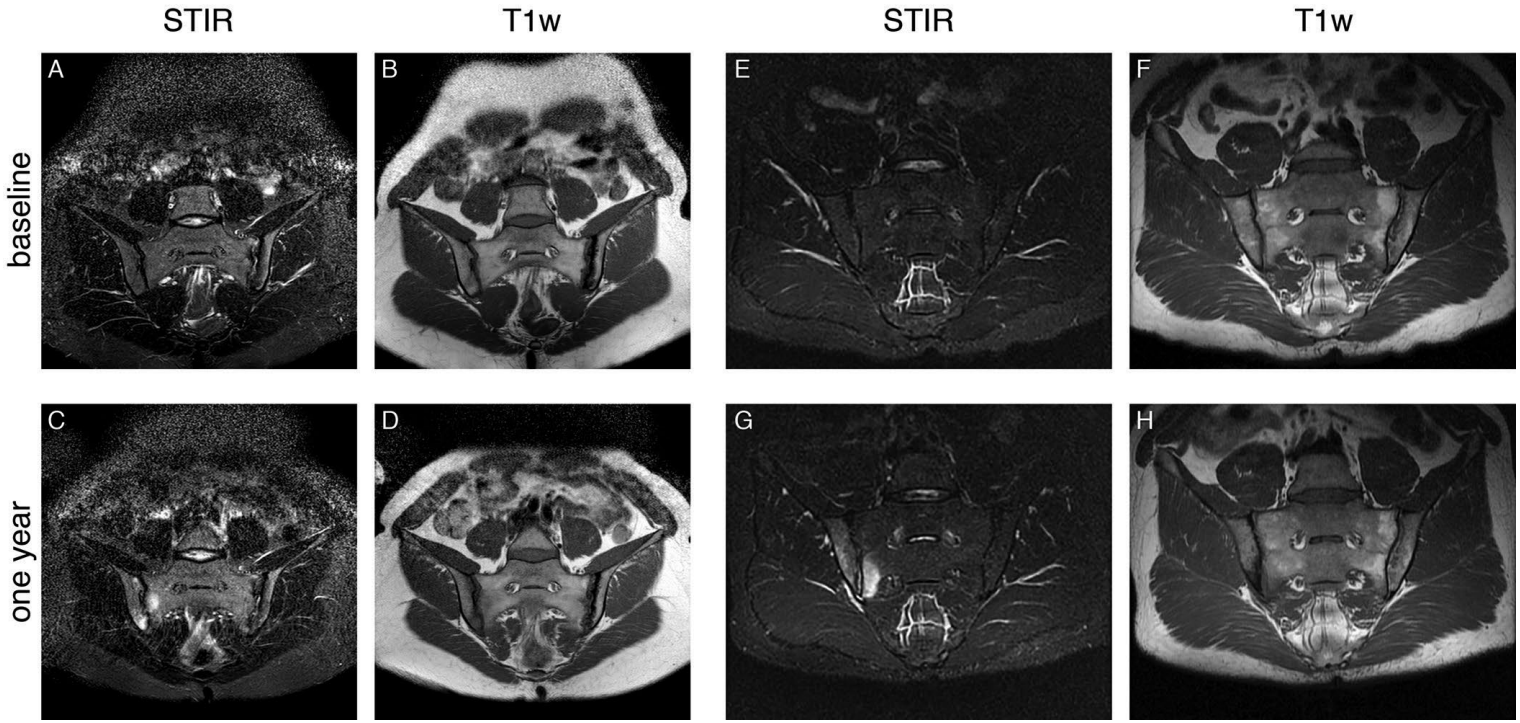
Supplementary Figure 1b: Cumulative probability plot of baseline and 1 year-SPARCC-scores in which patients were grouped according to either positivity or negativity according to the ASAS-definition – *reader 2*

ASAS, Assessment of SpondyloArthritis; axSpA, axial spondyloarthritis; BL, baseline; SPARCC, SPondyloArthritis Research Consortium of Canada.



Supplementary Figure 2a: Examples of patients with a change in MRI-SI ASAS status over 1 year time: MRI-SI ASAS positive (baseline) to MRI-SI ASAS negative (one year) (n=2)

STIR, short-tau inversion recovery; T1w, T1 weighted sequence; MRI-SI, magnetic resonance imaging of the sacroiliac joints; ASAS, Assessment of SpondyloArthritis international Society.



Supplementary Figure 2b: Examples of patients with a change in MRI-SI ASAS status over 1 year time: MRI-SI ASAS negative (baseline) to MRI-SI ASAS positive (one year) (n=2)

STIR, short-tau inversion recovery; T1w, T1 weighted sequence; MRI-SI, magnetic resonance imaging of the sacroiliac joints; ASAS, Assessment of SpondyloArthritis international Society.

9

The HLA-B27+/HLA-B*4001+ high risk ankylosing spondylitis genotype in early back pain patients suspected of axial spondyloarthritis: prevalence and association with spondyloarthritis features

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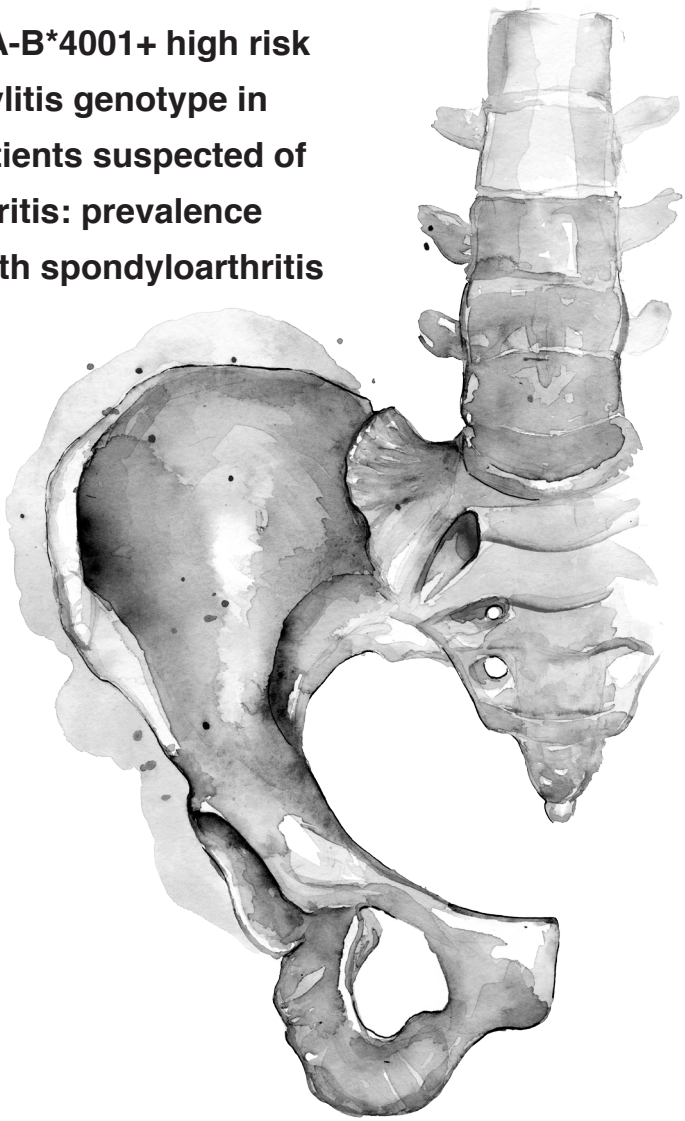

Submitted

ABSTRACT

Objective

HLA-B27 accounts for only a small part of the genetic risk for axSpA. Earlier studies have shown that the HLA-B27+/HLA-B*4001+ genotype has a high specificity for AS. Prevalence of this genotype was assessed in two cohorts of patients with chronic back pain suspected of axSpA.

Methods

Patients from the DESIR- (inflammatory back pain: ≥3 months, ≤3 years, age<50 years) and SPACE-cohort (back pain: ≥3months, ≤2 years, onset<45 years) were included as cases. Randomly selected healthy blood-bank donors from the Netherlands and France were used as controls. After DNA isolation from whole blood samples, a total of 854 patients (DESIR: 582; SPACE: 272) and 15761 controls (France: 10177; Netherlands: 5584) were genotyped for the presence of HLA-B27 and HLA-B*4001.

Results

The HLA-B27+/HLA-B*4001+ genotype was significantly more common in early back pain patients (DESIR 3.3% and SPACE 4.8%) than in controls (0.4% in both cohorts, p<0.001). HLA-B27+/HLA-B*4001+ patients showed a high percentage of radiographic sacroiliitis (DESIR 42% and SPACE 15% but were relatively similar to HLA-B27+/HLA-B*4001- back pain patients in terms of radiographic sacroiliitis (DESIR 27.6% and 16.5%) and to a lesser extent sacroiliitis on MRI. While comparing the mean number of SpA-features (surrogate for an increased likelihood of axSpA) no differences were seen between HLA-B27+/HLA-B*4001+ (DESIR: 2.6, SPACE: 3) and HLA-B27+/HLA-B*4001- (DESIR: 2.7, SPACE: 3.2) patients.

Conclusions

The HLA-B27/HLA-B*4001 high risk genotype was common in early back pain patients suspected of axSpA but as HLA-B27+/HLA-B*4001+ patients were similar to HLA-B27+/HLA-B*4001- patients our results suggest that combined testing for HLA-B27 and HLA-B*4001 has no added value in the early detection of axSpA.

INTRODUCTION

Susceptibility to ankylosing spondylitis (AS) is largely due to genetic factors. More than fifty years ago, the tendency of AS to recur within families was documented.[1] By means of family aggregation studies, it is estimated that genetic risk factors contribute to 80-90% of the susceptibility to AS. This is supported by studies, which have shown that concordance rates in monozygotic (50-75%) twins and dizygotic twins (15%) are markedly higher than the disease risk in the population at large.[2,3]

HLA-B27 (a major histocompatibility class (MHC) I molecule) is known to be the major genetic risk factor for AS. The association with the HLA-B27 gene was recognized 40 years ago and since then HLA-B27 is the strongest known risk factor for the disease.[4-6] However, only 5-6% of the HLA-B27 positive people in the general population will develop spondyloarthritis[7] and the overall contribution of HLA-B27 to AS heritability is estimated at 23.3%.[8] This suggests that HLA-B27 by itself is not sufficient for development of the disease, supporting the contribution of additional genes. In recent history, several large genome-wide association studies (GWAS) have been carried out, leading to the discovery of many new genetic risk factors.

Currently, over 30 genetic loci (both inside and outside the MHC) have been described to be operative in AS susceptibility. Within the MHC complex HLA-B*4001 (an allele that corresponds to HLA-B60 at the serological or protein level) is identified to be another genetic risk factor for AS. HLA-B60 was shown to be increased in HLA-B27 positive AS patients in five independent data sets in 1989.[9] More recently, this association was confirmed in the UK, the Netherlands and in Taiwan.[10-12] In 2013, epistasis between HLA-B27 and HLA-B*4001 has been reported to associate with increased risk of AS in Caucasians, with a very high relative excess risk. [11] The epistatic interaction is not reproduced in all studies, but the high specificity of the combined genotype was found in all three previously mentioned studies (sensitivity: 10.1%, 18.2%, 18.7%, specificity: 99.7%, 99.6%, 98.7%).[10-12]

Axial SpondyloArthritis (axSpA) is an umbrella term for a group of rheumatic diseases characterised by inflammation of the axial skeleton: sacroiliac (SI) joints and vertebral column. An important differentiation is made between radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA). In r-axSpA, sacroiliitis is visible on x-rays of the sacroiliac (SI) joints and the corresponding modified New York (mNY) criteria for AS are often used in studies and drug trials. But, axSpA can also be present in patients without radiographic changes but with active sacroiliitis being present on MRI (nr-axSpA). Axial SpA is a relatively uncommon disease (r-axSpA has an estimated pooled prevalence between 0.02%-0.35%, variation in reported prevalence estimates around the world)[13] presenting

with a very common complaint: 60-80% of the general population report back pain at some point in their lives.[14] As the clinical presentation of axSpA is heterogeneous and no single unique feature exists to identify axSpA from patients with back pain due to other causes, early diagnosis of axSpA is challenging.[15] In recent cohort studies of back pain patients at increased risk of axSpA have been set up to follow these patients prospectively over time.

There is a potential role for biomarkers to assist in the diagnostic process of axial SpA, including genetic diagnostic tests. As previously mentioned, the combined HLA-B27+/ HLA-B*4001+ genotype has been shown to be very specific for AS. However, this has only been investigated in late stage AS patients. The aim of this study is to assess the added value of HLA-B27/HLA-B*4001 in the detection of early axSpA. Therefore, we study the prevalence of the HLA-B27+/HLA-B*4001+ in two unique cohorts of patients with early back pain suspected of axSpA and studied the correlation of the genotype with other SpA-features.

METHODS

Patients and controls

Patients from the DEvenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort and SPondyloArthritis Caught Early (SPACE) cohort were included as cases. Both cohorts are described extensively elsewhere.[16,17] DESIR is a longitudinal cohort study, with patients included from 25 participating centres in France. Patients (aged >18 years and <50 years) with inflammatory back pain (IBP) with a duration of ≥3 months but <3 years are included in the study. IBP was defined according to either the Calin or the Berlin criteria.[18,19] Patients were only included in the cohort if the treating rheumatologist had a suspicion of axSpA defined as a score of ≥5 on a 0-10 scale (0: not suggestive of axSpA and 10: very suggestive of axSpA). The database for the baseline data used for this analysis was locked on 30 October 2012.

In contrast to the DESIR-cohort that includes only patients with IBP, the SPACE-cohort includes patients with chronic back pain (of a short duration (≥3 months but ≤ 2 years, onset <45 years). SPACE is an on-going inception cohort and patients are recruited in several centres across Europe and data from the following four participating centres were included in the current analysis: the Netherlands (Leiden, Gouda), Norway (Oslo) and Italy (Padua). Both studies fulfilled Good Clinical Practice (GCP) Guidelines and were approved by local medical ethical committees in all participating centres. Before inclusion, written informed consent was obtained from all patients.

Two control groups were used as a comparison. HLA-B typing from randomly selected, unrelated, healthy blood bank donors from the Netherlands[11] were used as controls for the

SPACE cohort and blood bank donors from France were used as controls for the DESIR cohort.

Diagnostic work-up

Patients in the SPACE and DESIR cohort underwent a full diagnostic work-up at baseline including MRI and conventional radiographs of the sacroiliac joints, and the assessment of all other SpA-features, in agreement with descriptions provided by the Assessment of SpondyloArthritis international Society (ASAS).[20] To define a patient as having ankylosing spondylitis, fulfilment of the modified mNY criteria is mandatory.[21] Radiographic sacroiliitis according to the mNY criteria was defined as bilateral grade ≥2 or unilateral ≥3. MRIs of the sacroiliac joints (MRI-SI) were considered positive according to the ASAS definition for a positive MRI.[22,23] Both radiographs and MRIs were reviewed by two experienced central readers per cohort, blinded for clinical data and the other imaging modality. In case of disagreement on mNY- or MRI-SI ASAS-positivity between the two initial readers, a third reader served as adjudicator. Images were marked positive if two out of three readers agreed.

DNA isolation and genotyping

HLA-B27 and HLA-B*4001 genotype data were collected from both patients and healthy controls. HLA-B27 typing was performed with sequence-specific primers on genomic DNA with real-time polymerase chain reaction using SYBR Green. In a total volume of 5 *µl* 10 ng, gDNA was mixed with 2.5 *µL of SYBR Select Master Mix (ThermoFisher Scientific, Breda, The Netherlands),* and 0.05 **µL** of a 100 nM primer solution mix was added. Primermix consists of both forward primer (5′-GCT ACG TGG ACG ACA CGC T) and reverse primer (5′-GCG CCC GCG GCT CCT CT). All reactions take place in a 384-well micro-plate and was measured by a CFX-384 ThermoCycler (Biorad Laboratories) with the following protocol: 95.0°C for 3 min followed by 40 amplification cycles (95.0°C for 0:05; 66.8°C for 0:10); standard melting curves.[24] Fluorescence data were analysed by CFX Manager Software Version 3.1 (Bio-Rad). For HLA-B*4001 two separate PCRs are used with the same PCR reaction mix as HLA-B27. PCR1: forward primer (5'-AGA TCT CCC AGC GCA AGT T) and reverse primer (5'- TCA GCG CGC TCC AGC TTG) with the following protocol: 95.0°C for 3 min followed by 40 amplification cycles (95.0°C for 0:05; 60.7°C for 0:10); standard melting curves.PCR2: forward primer (5'- GGG AGC CCC GCT TCA TCA CC) and reverse primer (5'-GGC TCC TTC CTC GGA CTC GT) with the following protocol: 95.0°C for 3 min followed by 40 amplification cycles (95.0°C for 0:05; 61.3°C for 0:10); standard melting curves. In blood donors who served as controls, HLA-AB typing was performed using PCR with sequence specific primers (SSP) using commercially available kits.[25]

Statistical analysis

Associations with the high-risk genotype were calculated for patients in both cohorts versus controls. Therefore, patients and controls were categorised into four strata based on both HLA-B27 and HLA-B*4001 positivity or negativity in a 4 by 2 table. With the disease risk in the HLA-B27-/HLA-B*4001- stratum in patients and controls as a reference (1), odds ratios for the risk of disease were calculated for the three remaining strata: HLA-B27+/HLA-B*4001+, HLA-B27+/HLA-B*4001-, HLA-B27-/HLA-B*4001+. For patients stratified by HLA-B typing, disease characteristics were calculated using descriptive statistics. Thereafter, the clinical phenotype of the non-AS patients with the HLA-B27+/HLA-B*4001+ genotype present was described, mainly evaluating the SpA-features present. The analyses were performed in STATA 12.0.

RESULTS

A total of 16615 subjects were analysed: 854 patients with chronic back pain suspected of having axSpA (DESIR: 582, SPACE: 272) and 15761 controls (living in France: 10177, living in the Netherlands: 5584).

First, we investigated the presence of the HLA-B27+/HLA-B*4001+ genotype in the two cohorts (results are depicted in Table 1). In DESIR, the HLA-B27+/HLA-B*4001+ genotype was present in 3.3% (n=19) of the patients and in 0.4% of the controls (odds ratio (OR) 9.5; 95% confidence interval (CI) 5.4-16.7; p<0.0001). In SPACE, the high-risk genotype was found in 4.8% of patients (n=13) and in 0.4% of controls (OR 12.7; 95% CI 6.3-25.5; p<0.0001). Nearly all of the patients with the HLA-B27+/HLA-B*4001+ genotype (94.7% (DESIR) and 100% (SPACE)) were Caucasoid (not shown).

Table 1: Presence of the HLA-B27+/HLA-B*4001+ genotype in two cohorts of chronic back pain (CBP) patients and controls

	DESIR	**Controls**
HLAB27+/HLA-B*4001+	19 (3.3%)	36 (0.4%)
HLAB27+/ HLA-B*4001-	319 (54.8%)	832 (8.2%)
HLAB27-/ HLA-B*4001+	11 (1.9%)	936 (9.2%)
HLAB27-/ HLA-B*4001-	233 (40.0%)	8373 (82.3%)
Total	582 (100%)	10177 (100%)
	SPACE	**Controls**
HLAB27+/HLA-B*4001+	13 (4.8%)	22 (0.4%)
HLAB27+/ HLA-B*4001-	85 (31.3%)	381 (6.8%)
HLAB27-/ HLA-B*4001+	25 (9.2%)	654 (11.7%)
HLAB27-/ HLA-B*4001-	149 (54.8%)	4527 (81.1%)
Total	272 (100%)	5584 (100%)

DESIR: OR 9.5 (95% CI: 5.4-16.7; p<0.0001).
SPACE: OR 12.7 (95% CI: 6.3-25.5; p<0.0001).
HLA-B27, human leukocyte antigen B27; HLA-B*4001, human leukocyte antigen B*4001; DESIR, DEvenir des Spondyloarthrites Indifférenciées Récentes; SPACE, SPondyloArthritis Caught Early.

Disease characteristics of the two cohorts are depicted in Table 2. The data shown are stratified according to the presence of HLA-B27 and HLA-B*4001. In Table 2: data from the four strata taken together, patients had a mean age of 31.5 (DESIR) and 31.3 (SPACE) years. Mean symptom duration was 18.2 months in DESIR and 13.0 months in SPACE. Of the 19 patients in the DESIR cohort with the high-risk genotype, 8 (42.1%) had radiographic sacroiliitis (mNY). In the SPACE cohort, radiographic sacroiliitis according to the mNY-criteria was seen in 2/13 (15.4%) patients with the high risk HLA-B27+/HLA-B*4001+ genotype (Table 2).

Of the HLA-B27+/HLA-B*4001+ and HLA-B27+/HLA-B*4001- patients in both cohorts the majority was male, whereas in the two other strata females were overrepresented. A positive family history of SpA was more frequent in HLA-B27+/HLA-B*4001+ and HLA-B27+/HLA-B*4001- patients, compared to patients in the two other strata.

Recently published data of the SPACE cohort have pointed out that an increasing number of SpA-features is associated with an increased likelihood of axSpA although this association was not absolute.[26] Comparing the mean total number of SpA features (SD) between HLA-B27+/HLA-B*4001+ with HLA-B27+/HLA-B4001- patients revealed no notable differences: being 3 (1) in the HLA-B27+/HLA-B*4001+ patients and 3.2 (1.1) in the HLA-B27+/HLA-B4001- patients of the DESIR cohort (SPACE: 2.6 (1.7) and 2.7 (1.6) respectively). Overall, while comparing disease characteristics of patients amongst the four strata, differences in disease characteristics were seen. But, differences turned out to be marginal when comparing HLA-B27+/HLA-B*4001+ with HLA-B27+/HLA-B4001- patients.

Likewise, comparing the percentage of patients with any positive imaging (defined as minimally one positive imaging modality: sacroiliitis on radiographs according to the mNY definition and/or a positive MRI according to the ASAS definition) revealed differences between the HLA-B27 positive versus negative group, with more patients having positive imaging in the HLA-B27 positive patients. (DESIR odds ratio (OR) 1.9; 95% confidence interval (CI) 1.3 to 2.7; p<0.001 and SPACE OR 4.0; 95% CI 2.1 to 7.5; p<0.001.). However, positive imaging was not significantly different in HLA-B27+/HLA-B*4001+ and HLA-B27+/HLA-B4001-patients (DESIR OR 0.9; 95% CI 0.3 to 3.2; p 0.9 and SPACE OR 1.6; 95%CI 0.5 to 5.2; p=0.4).

Table 2: Disease characteristics of recent onset chronic back pain patients included in the DESIR and SPACE cohort stratified by HLA-B typing

	DESIR (n=582)				SPACE (n=272)			
Number of patients (per genotype)	**19**	**319**	**11**	**233**	**13**	**85**	**25**	**149**
HLA-B27 status	**+**	**+**	**-**	**-**	**+**	**+**	**-**	**-**
HLA-B*4001 status	**+**	**-**	**+**	**-**	**+**	**-**	**+**	**-**
Age (years) at inclusion, mean ±SD	32.8 (5.4)	30.0 (7.1)	35.4 (7.3)	31.6 (7.1)	28.0 (7.8)	29.8 (8.2)	32.1 (9.2)	32.3 (8.4)
Male, n (%)	11 (57.9)	171 (53.6)	2 (18.2)	93 (39.9)	8 (61.5)	43 (50.6)	6 (24.0)	40 (26.9)
Caucasoid, n (%)	18 (94.7)	290 (90.9)	7 (63.6)	203 (87.1)	13 (100)	74 (97.4)	20 (90.9)	123 (91.1)
Symptom duration (months) , mean ±SD	18.2 (10.5)	18.0 (10.6)	17.2 (2.2)	18.4 (10.6)	11.5 (5.6)	12.2 (7.2)	14.6 (8.1)	13.3 (7.3)
Positive family history SpA, n (%)	7 (36.8)	96 (30.1)	2 (18.2)	41 (17.6)	9 (69.2)	46 (54.8)	8 (32.0)	37 (24.8)
IBP, n (%)	19 (100)	319 (100)	11 (100)	233 (100)	8 (61.5)	63 (75.0)	14 (56.0)	89 (59.7)
Good response to NSAIDs, n (%)	15 (79.0)	268 (84.0)	6 (54.6)	170 (73.0)	6 (46.2)	37 (44.1)	9 (36.0)	35 (23.8)
Peripheral arthritis, n (%)	2 (10.5)	56 (17.6)	1 (9.1)	41 (17.6)	3 (23.1)	16 (19.1)	2 (8.0)	20 (13.4)
Dactylitis, n (%)	0 (0)	42 (13.2)	3 (27.3)	29 (12.5)	1 (7.7)	5 (6.0)	1 (4.0)	6 (4.0)
Enthesitis, n (%)	8 (42.1)	141 (44.2)	5 (45.5)	128 (54.9)	2 (15.4)	21 (25.0)	3 (12.0)	18 (12.1)
Uveitis, n (%)	3 (15.8)	26 (8.2)	1 (9.1)	10 (4.3)	1 (7.7)	12 (14.3)	1 (4.0)	6 (4.0)
Psoriasis, n (%)	2 (10.5)	48 (15.1)	2 (18.2)	38 (16.3)	1 (7.7)	8 (9.5)	2 (8.0)	15 (10.1)
IBD, n (%)	1 (5.3)	11 (3.5)	0 (0)	17 (7.3)	0 (0)	3 (3.6)	5 (20.0)	15 (10.1)
Elevated CRP, n (%)	8 (47.1)	93 (31.0)	3 (30.0)	64 (28.8)	3 (23.1)	18 (22.0)	3 (12.0)	25 (16.8)
Total number of SpA features*, mean (SD)	3 (1)	3.2 (1.1)	2.8 (1.3)	3.0 (1.1)	2.6 (1.7)	2.7 (1.6)	1.9 (1.6)	1.8 (1.5)
Sacroiliitis radiograph (mNY), n (%)	8 (42.1)	88 (27.6)	1 (9.1)	29 (12.5)	2 (15.4)	14 (16.5)	2 (8.0)	9 (6.0)
Positive MRI (ASAS definition), n (%)	9 (47.4)	133 (41.7)	2 (18.2)	66 (28.3)	2 (15.4)	22 (25.9)	3 (12.0)	9 (6.0)
ASAS axSpA classification, n (%)	19 (100)	310 (97.2)	4 (36.4)	87 (37.3)	9 (69.2)	73 (85.9)	3 (12.0)	12 (8.1)
Any positive imaging (MRI and/or mNY), n %	11 (57.9%)	151 (47.3%)	3 (27.3%)	77 (33.0%)	4 (30.8%)	28 (32.9%)	4 (16%)	15 (10.1%)

*Spondyloarthritis (SpA) features after medical history taking, physical examination and measurement of acute phase reactants, but before HLA-B27 testing and imaging.

HLA-B27, human leukocyte antigen B27; HLA-B*4001, human leukocyte antigen B*4001; SpA, spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory drugs; IBP: inflammatory back pain; IBD, inflammatory bowel disease; CRP, C-reactive protein; mNY, modified New York; ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; DESIR, DEvenir des Spondyloarthrites Indifférenciées Récentes; SPACE, SPondyloArthritis Caught Early.

In both cohorts, 11 patients have the high-risk genotype but did not fulfil the mNY-criteria for AS. The characteristics and SpA-features of these patients are shown in Tables 3 and 4. The number of other present SpA-features which influences the likelihood of axSpA (in absence of one single distinguishing feature and diagnostic criteria) varied between patients (Tables 3 and 4). For example, patient number 5 in DESIR has five additional SpA-features: a history

of uveitis, enthesitis, elevated CRP or ESR and a good response to NSAIDs. Likewise, patient 11 in SPACE is highly suspicious to have axSpA being HLA-B27 positive and having 6 other SpA-features. On the contrary, patient 6 (SPACE) has no single other SpA-feature which makes axSpA unlikely. Equally, a positive family history as the only single SpA-feature in HLA-B27 positive patients (DESIR: 10, SPACE: 5) is not very suggestive for axSpA.

DISCUSSION

In these two cohorts of early inflammatory and chronic back pain patients, the high risk AS genotype (HLA-B27+/HLA-B*4001+) was found to be increased compared to controls. To our knowledge high-risk or complex SpA genotypes have never been studied in early back pain patients suspected of axSpA. Studies that have been earlier performed, were all performed in ankylosing spondylitis patients only: i.e. a much more homogeneous group than patients with axSpA. This is of course pivotal for the identification of novel genetic associations. However, the 'real-life' situation at the outpatient clinic is different and confirmation in more heterogeneous cohorts is needed to investigate its possible diagnostic value. A strength of this current study is that we assessed the prevalence of the HLA-B27+/HLA-B*4001+) high-risk genotype in two independent cohorts of patients with chronic back pain, suspected for axSpA. The fact that images in each cohort were scored by two well-trained readers, blinded for clinical data and genotype status, also adds to the credibility of the findings.

Of the patients with the high-risk genotype, even with a short symptom duration, a considerable proportion already had radiographic sacroiliitis. Moreover, objective measures for inflammation (elevated CRP, positive MRI-SI) were also common in HLA-B27+/HLA-B*4001+ patients. However, all these observations were also true for patients with HLA-B27 but without HLA-B*4001. In general, differences in disease characteristics were seen while comparing the four strata, but differences were insignificant while comparing HLA-B27+/HLA-B*4001+ with HLA-B27+/HLA-B4001- patients. Therefore, these data indicate that there is no added value of HLA-B*4001 testing compared to testing for HLA-B27 alone in this population of patients with back pain referred to a rheumatologist.

Table 3: Clinical phenotype of non-AS patients with HLA-B27+/HLA-B*4001+ genotype (DESIR)

Patient ID	Gender	Age	ASAS axSpA classification	IBP	NSAIDs good reaction	Periph. arthritis	Raised CRP /ESR	Enthesitis	IBD	Positive family history	Uveitis	Dactylitis	Psoriasis	HLA-B27	MRI ASAS	mNY-criteria
1	Female	32	Yes	1	1	0	0	1	0	1	0	0	0	1	0	0
2	Female	31	Yes	1	1	0	0	0	0	1	0	0	0	1	0	0
3	Male	41	Yes	1	1	0	0	1	0	0	0	0	1	1	0	0
4	Female	32	Yes	1	1	0	1	1	0	0	0	0	0	1	0	0
5	Male	37	Yes	1	1	0	1	1	0	0	1	0	0	1	0	0
6	Male	36	Yes	1	1	0	0	0	0	0	0	0	0	1	1	0
7	Male	36	Yes	1	0	0	1	1	0	0	0	0	1	1	0	0
8	Female	28	Yes	1	1	0	1	1	0	0	1	0	0	1	1	0
9	Male	22	Yes	1	0	0	0	0	0	0	0	0	0	1	1	0
10	Female	39	Yes	1	0	0	0	0	0	1	0	0	0	1	0	0
11	Male	23	Yes	1	1	0	0	0	0	1	1	0	0	1	0	0

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; IBP: inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; periph. arthritis, peripheral arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; HLA-B27+, human leukocyte antigen B27 positive; MRI, magnetic resonance imaging; mNY-criteria, modified New York criteria.

Table 4: Clinical phenotype of non-AS patients with HLA-B27+/HLA-B*4001+ genotype (SPACE)

Patient ID	Gender	Age	ASAS axSpA classification	IBP	NSAIDs good reaction	Periph. arthritis	Raised CRP /ESR	Enthesitis	IBD	Positive family history	Uveitis	Dactylitis	Psoriasis	HLA-B27	MRI ASAS	mNY-criteria
1	Female	24	Yes	0	1	0	1	0	0	1	0	0	0	1	0	0
2	Male	37	Yes	1	1	1	0	0	0	0	0	0	0	1	0	0
3	Male	26	Yes	1	0	0	0	0	0	1	0	0	0	1	0	0
4	Male	27	Yes	1	0	0	0	0	0	1	0	0	0	1	1	0
5	Female	36	No	0	0	0	0	0	0	1	0	0	0	1	0	0
6	Male	29	No	0	0	0	0	0	0	0	0	0	0	1	0	0
7	Female	22	Yes	0	1	0	0	0	0	1	0	0	1	1	0	0
8	Male	22	Yes	1	0	0	0	0	0	1	0	0	0	1	0	0
9	Male	43	Yes	1	1	1	1	0	0	1	0	0	0	1	1	0
10	Female	18	No	0	0	0	0	0	0	1	0	0	0	1	0	0
11	Male	24	Yes	1	1	1	1	1	0	0	0	1	0	1	0	0

ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; IBP: inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; periph. arthritis, peripheral arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; HLA-B27+, human leukocyte antigen B27 positive; MRI, magnetic resonance imaging; mNY-criteria, modified New York criteria.

Despite the lack of diagnostic potential, it will be interesting to investigate if the high-risk genotype is associated with disease progression such as radiographic damage progression in the two cohorts. Relatively little is known about long term radiographic progression in early axial spondyloarthritis (both in the spine and sacroiliac joints).

It is important to realise that patients in both cohorts were already *referred* to a rheumatologist. This pre-selection of patients is in itself not a problem, though certain symptoms or 'red flags' might have led to referral and therefore pre-test probabilities will be higher which could underestimate the effect of testing for the combined high risk genotype in a population of unselected back pain patients. A next step could be to investigate if the high-risk genotype could help identifying patients at risk of axSpA. This could be useful in population studies with high a prevalence of chronic back pain not caused by SpA where a high specificity is a needed.

In the current study, we only looked at the presence of HLA-B*4001 but other AS high risk genotypes are known. It has been previously shown that HLA-B27 homozygosity is associated with an increased risk of AS.[27] Unfortunately, our current PCR technique is not suited to test for HLA-B27 homozygosity in patients. Gene-gene interactions between HLA-B27 and ERAP1 have also been studied and a high specificity is suggested.[28] Regrettably, for the current study we did not have controls available to investigate the prevalence of a combined HLA-B27/ERAP genotype or combinations of HLA-B27, HLA-B*4001 and ERAP1 SNPs.

In summary, although AS was common in HLA-B27+/HLA-B*4001+ chronic back pain patients, our results show that HLA-B27+/HLA-B*4001+ testing has no incremental value in the diagnostic process of axSpA by a rheumatologist above HLA-B27+ testing alone. High-risk genotypes might have value in screening back pain patients in the population, but this needs to be investigated further.

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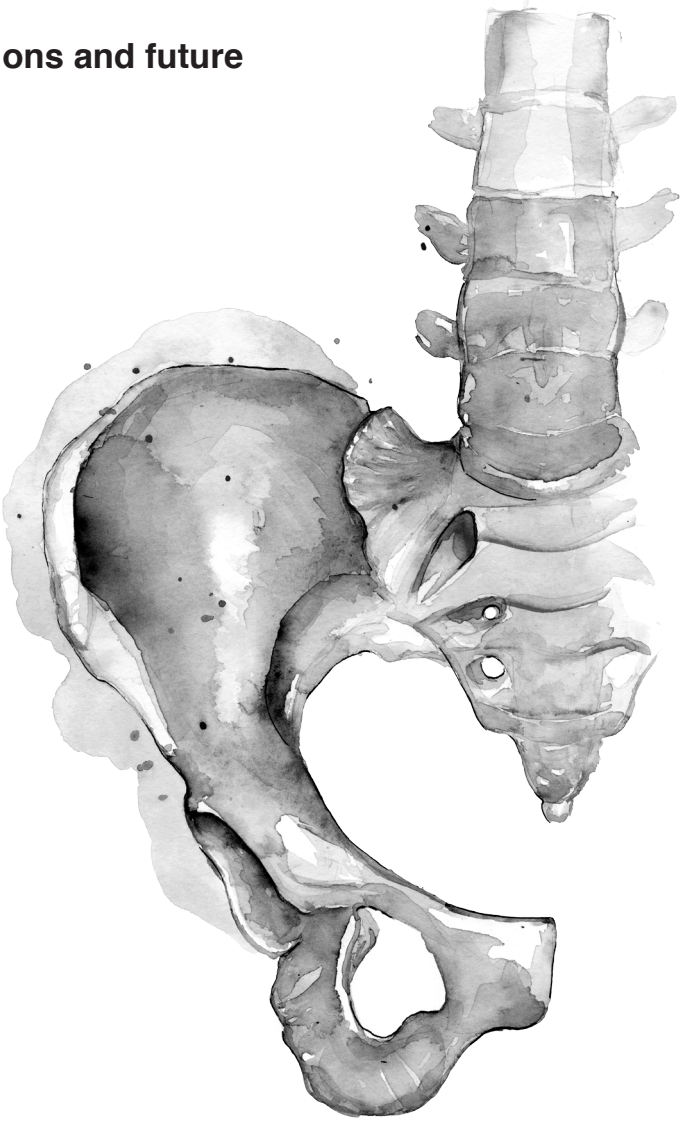
Summary, conclusions and future perspectives



The studies described in this thesis were all centred around the same aim: the early recognition of axial spondyloarthritis (axSpA) and a minimization of the diagnostic delay. An important step in tackling these issues was that experts in the field have designed prospective cohort studies in which consecutive patients with either chronic or inflammatory back pain (the latter being the most common first symptom) of short duration are included and followed up in a standardized manner with imaging performed at certain pre-set times. This allows us to obtain information on who will develop axSpA and who will not. Those cohort studies provide valuable information on the early detection and disease course of axSpA and form the basis of the research presented in this thesis.

The first part of this thesis covered two studies on the performance of different classification criteria sets in a worldwide clinical setting and the necessity of performing additional investigations (HLA- B27 testing; sacroiliac joint imaging) in a subgroup of patients with only one or even zero SpA features (i.e. a low pre-test probability of having axSpA). Subsequently, the focus shifted to the role of imaging in the early detection of the disease. First, the literature on recent advances in sacroiliac joint imaging (both conventional x-rays and MRI) was reviewed; this formed partly the starting point for a consensus exercise by ASAS which resulted in an update of the existing definition for a positive MRI for classification of axSpA. Then, the additional value of using structural lesions on MRI in the ASAS axSpA classification criteria was assessed. Thereafter, we zoomed in on the diagnostic process again; the usefulness of repeating an MRI of the sacroiliac joints (after three months or one year) with regards to diagnosis of patients with chronic back pain suspected of axSpA was assessed. In the last part of this thesis, the prevalence of the HLA-B27+/HLA-B*4001+ genotype was assessed in two early axSpA cohorts; and its potential role in the diagnostic process was discussed.

The studies presented in this thesis were conducted in two prospective cohort studies and one study with a cross-sectional design. The two cohort studies are the SPondyloArthritis Caught Early (SPACE) cohort and the DEvenir des Spondyloarthropathies Indifférenciées Récentes (DESIR) cohort. The cross-sectional study mentioned is the Assessment of SpondyloArthritis international Society COMOrbidities in SPondyloArthritis (ASAS-COMOSPA) study. SPACE is an ongoing observational cohort study in which patients aged ≥16 years with short-term chronic back pain (CBP of ≥3 months, ≤2 years and an onset of <45 years) referred to a rheumatologist are included.[1] Patients are recruited from several participating centres in four European countries: the Netherlands, Norway, Italy and Sweden. Follow-up is performed in a standardised manner with the collection of clinical and imaging data at pre-set times (baseline, three months, one year, two years, thereafter every two years). Baseline and one-year follow-up data were used for this thesis. DESIR is a longitudinal cohort study in which patients aged 18-50 years with inflammatory back pain (IBP) are included from 25 regional

centres in France.[2] The presence of IBP (according to the Calin or Berlin criteria)[3,4] and a back pain duration of ≥ 3 months and <3 years was required for inclusion. Besides the mandatory presence of IBP, a patient was only included if the rheumatologist responsible for enrolment had a level of confidence about the diagnosis of SpA of at least 5 (0-10 scale: 0 is not confident and 10 means very confident). The cohort is aiming for a 10-year follow-up, but for this thesis only baseline data were used. The SPACE cohort has important similarities to DESIR, though an important difference is that in DESIR patients with IBP are included, whereas SPACE includes patients with chronic back pain, not necessarily inflammatory back pain. Furthermore, in DESIR the presence of an axSpA diagnosis is at least probable whereas this is not the case in SPACE. A practical difference is that SPACE is an ongoing cohort study; whereas inclusion in DESIR is currently closed and was performed between December 2007 and April 2010. The ASAS-COMOSPA study is a study initiated by ASAS aimed to evaluate the prevalence of comorbidities and risk factors in SpA patients (both axial and peripheral) in different countries worldwide and to evaluate the gap between available recommendations and daily practice for management of these comorbidities. It is an international, observational study with a cross-sectional design in which patients diagnosed with SpA (according to the treating rheumatologist) were included.[5] Inclusion took place in 22 countries from five different regions across the world: Asia, North Africa, Latin America, North America, Central Europe and Western Europe. The multi-nationality of the study; the high number of included patients raised the opportunity for ancillary studies like the one described in this thesis.

In this final chapter, we summarize the main findings of the studies presented in this thesis and we will place them in a broader perspective. We will also discuss future perspectives and formulate research questions that could be relevant to assess in the years ahead of us.

PART I: EARLY RECOGNITION AND CLASSIFICATION CRITERIA

Classification criteria are frequently evaluated in restricted patient populations; very often cohort studies with strict inclusion criteria in specialised clinics, which leads automatically to fairly homogeneous groups of patients.[6-9] This is of course essential for the proof-of-concept of evaluating the performance of those criteria, but at the same time it poses the question how these classification criteria would perform in a setting which closely resembles the situation of daily clinical practice: a situation where a heterogeneous assembly of patients with chronic back pain presents to rheumatologists worldwide.

Classification criteria have all been developed using 'expert opinion' as the external standard in the absence of an indisputable gold standard. Pattern recognition forms the basis of this expert opinion: rheumatologists combine individual patient characteristics and presenting symptoms with their own knowledge about the pattern of disease (the so-called 'Gestalt'). It is therefore not difficult to understand that 'expert opinion' is not an unequivocal and homogeneous construct. It may potentially integrate different pictures of the disease which is even more comprehensible from a global perspective (diversity of patient populations and rheumatology training programmes).

In **chapter 2**, the performance of several classification criteria sets was tested in a worldwide population of patients. Patients were recruited from routine clinical practice in a large number of rheumatology clinics around the world. We investigated if rheumatologists worldwide *diagnose* a similar type of patients as having SpA by testing if patients fulfil similar criteria sets in the ASAS- COMOSPA study. This was done under the assumption that the more criteria sets a patients fulfils the higher the likelihood is that a patient with diagnosis of SpA truly *has* SpA. It was concluded that most patients with a clinical diagnosis of SpA fulfil several classification criteria sets and substantial overlap between criteria sets was seen which adds to the credibility and validity of the different criteria sets. In this case it is important to mention that this cohort is not a cohort of early disease, reflected by 65% modified New York criteria positivity. But despite the overlap of the various criteria sets, a substantial number of patients was being picked up by only one criteria set; namely the ASAS axSpA criteria.

Earlier studies already revealed that the ASAS criteria[10,11] which were released in 2009, outperformed other classification criteria such as the Amor[12] and ESSG[13] criteria in terms of a better sensitivity due to the presence of MRI in the imaging arm compared to other criteria sets developed in the pre-MRI era. When tested against experts' diagnosis the ASAS criteria represent the current 'Gestalt' better than the ESSG and AMOR criteria, that were designed decades ago before the introduction of MRI. Besides the fact that MRI findings are incorporated in the imaging arm of the ASAS axSpA-criteria which is not the case in any other criteria set; the ASAS criteria in general differentiate between axial and peripheral SpA. Although the ESSG and Amor criteria cover the whole spectrum of SpA and include a broader range of manifestations compared to the modified New York criteria (which will be discussed later), these criteria do not distinguish between axial and peripheral SpA. This differentiation is important though, for example when testing treatment strategies. Recently, a systematic literature review and meta-analysis was performed to summarise the evidence on the performance of the ASAS classification criteria.[14] The entire set of the ASAS SpA criteria yielded a high pooled sensitivity (73%) and specificity (88%). Similarly, good results were found for the axSpA criteria (sensitivity: 82%, specificity: 88%).

Nonetheless, rheumatologists and healthcare systems around the world have raised concerns regarding the criterion validity of the ASAS criteria and have posed the question if a modification of the criteria is needed. More explicitly, the specificity of the criteria is being questioned: it has been advocated that the clinical arm adds sensitivity to the axSpA criteria, while compromising on specificity. In other words, that patients fulfilling only the clinical arm should not be considered as having 'true axSpA' (mislabelling).[15,16] This contrasts sharply with the imaging arm, which had been broadly recognized and well-accepted. Therefore, in chapter 2 we have also compared disease characteristics of patients fulfilling the clinical and imaging arm. It was found that patients fulfilling the clinical arm were remarkably similar to patients fulfilling the imaging arm with respect to the presence of most SpA features. This finding is in line with earlier observations in the SPACE and DESIR cohort.[1,17] Also, in the ABILITY-1 trial (a randomized controlled trial performed in patients with non-radiographic axSpA to evaluate the efficacy and safety of adalimumab) there were no striking differences between patients who fulfilled the imaging arm and those who fulfilled the clinical arm of the ASAS axSpA criteria.[18] In these studies, it was also noted that patients in the different arms were not only remarkably similar with respect to the presence of SpA features, but also with respect to levels of disease activity (BASDAI and ASDAS). In the current ASAS-COMOSPA study, the relevance of the clinical arm was demonstrated once again.

Many patients in this study did not undergo MRI. This situation is (highly) compatible with daily clinical practice since MRI is relatively expensive and the availability can be limited. When MRI is not available, a substantial proportion of patients will remain unrecognized and the sensitivity of the criteria decreases. If the problem will be more prominent in women, who seem to be at a lower risk of radiographic progression (male gender was found to be a risk factor for developing radiographic sacroiliitis and therefore, for evolution from non-radiographic axSpA to radiographic axSpA) needs to be evaluated[19] as we observed that a positive MRI was less frequent in females in SPACE (see below). Another important issue is the fact that sacroiliac joint imaging (both conventional radiographs and MRI) is difficult to interpret, especially in clinical practice.[20-22] In the DESIR cohort, it was shown that both trained readers and local rheumatologists/radiologists agreed only moderately on the recognition of radiographic sacroiliitis. A significant proportion of patients that were labelled as having radiographic sacroiliitis by local readers was *not* confirmed by central readers (false positive).[21] In another study, disagreement amongst local and central readers on positive sacroiliac joint imaging (MRI and/or x-rays) was present in 28% of the patients.[20] Since imaging was marked positive more often by local readers, the specificity of the imaging arm is jeopardized (false-positivity). As was demonstrated by our study, many patients fulfil both the imaging and the clinical arm. Therefore, the risk of the above described 'misinterpretation' becomes less prominent in presence of the clinical arm.

Until recently, the validity of the ASAS criteria had only been studied in a cross-sectional setting in different cohorts[1,22,23] which means that the fulfilment of the criteria and the diagnosis of the rheumatologist (external standard) are assessed at the same time. In a sense, the metrics sensitivity and specificity are somewhat static, leaving aside *predictive* characteristics such as the probability of having SpA once the criteria are applied (post-test probability). It is essential to know if patients that were initially classified as axSpA will still be considered as having a SpA diagnosis after years of follow-up). Recently, data on the predictive validity of the ASAS criteria have been published[14] patients from the ASAS cohort were followed over 3-5 years and rheumatologists carefully reviewed their cases again. 93.3% of the patients that initially fulfilled the criteria would still be diagnosed as axSpA by the rheumatologist which leads to an excellent predictive validity and likewise suggests consistency of the criteria over time. Comparable results were found for the imaging arm (range: 94.5-96.5%) and clinical arm (range: 96.4-98.2%) and also considering those fulfilling the 'imaging arm' only (range: 85.1-86.7%) and clinical arm only (range: 87.9-92.9%). The negative predictive value was somewhat lower. However, since it is known that SpA features can change over time this might just reflect the natural disease course rather than revealing a negative test characteristic. These data on the predictive validity adds up to the robustness of the ASAS criteria. Since similar PPVs for both arms of the axSpA criteria were found, these data also support the view that the clinical arm comprises a group of patients who belong to the SpA spectrum as much as those fulfilling the imaging arm.

Due to the lack of diagnostic criteria, physicians may be tempted to use classification criteria as such. The same clinical, laboratory and imaging indices are used for classification and diagnosis, but clear differences exist in their application. Caution should be raised on using classification criteria as a check box to be ticked in order to make a diagnosis.[24,25] An essential step that is missed by simply counting SpA features, is the exclusion of other likely diagnoses (differential diagnostic thinking) and also negative findings not pointing in the direction of axSpA. As earlier explained classification criteria are designed for classification instead of diagnostic purposes and furthermore, should only be applied in patients diagnosed with SpA (not vice versa).Honesty demands the admission that in our studies classification was not applied only in diagnosed patients and with progressive insight we would have approached this differently. The problem of using classification criteria to make a diagnosis is especially problematic in case of ticking boxes, patients not seen by a rheumatologist and especially if the pre-test probability is low. In patients with a relatively high pre- test probability, such as in the studies described in this thesis where the pre-test probability is around 30%, the misdiagnosis is much less. Furthermore, in SPACE, exclusion of other likely diagnoses was done by the rheumatologist even before patients were presented to and thereafter included in SPACE. Plus, the fact that evaluation of SpA features was done by experts only. However,

this can still be seen as a relative weakness of the studies. Classification criteria are developed to get a clear yes/no answer, to create a rather homogeneous group of patients, usually for inclusion into a cohort or clinical trial. They ensure comparability across these studies, but it is difficult to capture the full range of disease presentations by any single set of criteria. As explained above, knowledge of the pre-test probability of having the disease is essential in diagnosis. In a cohort of patients with chronic back pain in a primary care physician setting, SpA was diagnosed in 5% of the cases and this is frequently used as the assumed pre-test probability of this disease. In the studies described in this thesis, we used the 5% pre-test probability to calculate disease probabilities. But, we performed our studies in a secondary (or even tertiary) care setting were the pre-test probability is expected to be higher compared to the primary care setting. Unfortunately, an estimation of the pre-test probability in this setting was unknown when the cohort was started, after a few years we investigated that it is around 30%. So, the pre-test probability of 5%, which we used, resulted in an underestimation of the post-test disease probability.

The diagnostic work-up of axSpA is a challenge; some of the arguments why this is the case did already come across earlier in this chapter. In general, the disease should be suspected in patients with chronic back pain (CBP) with onset before 45 years of age and a history of CBP that has been almost continuous for three months or more (sub-acute onset). This should prompt further evaluation to establish whether other SpA features are present.

The modified Berlin algorithm serves as a helpful tool to assist rheumatologists in the diagnosis of axSpA; and it should be applied in patients with CBP with age of onset <45 years.[26] The algorithm suggests that radiographs of the sacroiliac joints are advised in all referred patients with back pain with the features described above, regardless of the presence of other SpA features, and if negative all patients are assessed for the presence of other SpA features and tested for HLA-B27. In the study described in **chapter 3**, we aimed to investigate if HLA-B27 testing and imaging of the sacroiliac joints (by means of conventional radiographs and MRI) is necessary in a subgroup of patients with a low likelihood of axSpA: patients with zero or only one SpA feature after clinical examination and measurement of acute phase reactants. Surprisingly, a diagnosis of SpA was made in 18.4% (zero SpA features) and 17.9% (one SpA feature) of the patients. We were surprised of these relatively high percentages. Even in patients without a single SpA feature after clinical examination and acute phase reactants measurement, it was not possible to entirely rule out axSpA. It is relevant to keep in mind the population of patients in which the research question is investigated, which influences the pre-test probability. Patients included in the SPACE cohort are referred to a rheumatologist and certain red flags or other findings have precluded referral. In fact, more likely diagnoses are already excluded. Therefore, the results of this study should be restricted to patients with a higher pre-test probability; and therefore, cannot be automatically extrapolated or

generalized to for example the general practitioners' practice.

However, these nuances set aside, it is surprising that in these groups of patients with a low likelihood of the disease before testing, diagnosis is not that uncommon as expected beforehand. It can be questioned how realistic the majority of these diagnoses are. Imaging plays a pivotal role and is often decisive in whether or not making a diagnosis. This is well understandable since radiologic abnormalities feel as an objective sign of disease. But as an example, it feels like overshooting that in a female patient with back pain but zero other SpA features, a sole finding of sacroiliitis on radiographs is sufficient to establish a diagnosis. On the other hand, a diagnosis may still be justifiable because of features or symptoms that are outside the SpA features we examined, for example buttock pain, presence of structural lesions on MRI-SI or spinal inflammatory lesions. It might also have been the case that the modified Berlin algorithm is followed to stringently especially by less experienced rheumatologists (in training) in the field of axSpA. It should be stressed again that the ASAS modified Berlin algorithm is only a tool in aiding rheumatologists in diagnosing axSpA and can and should not replace a differential diagnostic procedure in patients with CBP. For example, the dominance of conventional radiographs in the modified Berlin algorithm is under debate. In general, discussion is on-going to what extent additional investigations should be performed in order to approve or disapprove a diagnosis and worries have been expressed if the current diagnostic work-up is not too extensive, mainly in patients with a low pre-test probability. Ideally we would aspire a tailored diagnostic process in which doctors should *only* perform specific investigations under certain motivations and be more resilient in specific patient groups with a low pre-test probability. Moreover, only follow-up of these patients will confirm if the diagnosis was correct and if imaging was interpreted correctly.

Sequential testing is also advocated in the modified Berlin algorithm. Although we have not tested the algorithm in the study described in chapter 3, we think that the role for MRI-SI may be a bit too confined. MRI-SI should only be performed in a very specific situation, which sharply contrasts to conventional radiography which is the broadly recognized first step in the algorithm. In a group of patients with short-standing complaints like the SPACE cohort it is however very likely that radiographic abnormalities have not yet developed which could possibly lead to a false-negative diagnosis if no other tests are performed. The recently published EULAR recommendations are a bit less conservative and recommend MRI-SI as an alternative first imaging method in for example young patients with a short symptom duration. In the later described chapter 8 we will assess the course of MRI-SI activity over one year and the identification of predicting factors for a positive MRI.

Future perspectives

The early diagnosis of axSpA by a rheumatologist is important and a main objective of this thesis. But one step back, identification of patients at an increased risk of axSpA which precedes this process is also essential. It is obvious that a late referral of patients to a rheumatologist contributes to the diagnostic delay. CBP is highly prevalent in the general population and axSpA is responsible for only 5% of the cases in the primary care setting. Effective referral strategies are highly warranted.

Therefore, increased disease awareness is also of critical importance both on doctor and patient level. Education is important to reach the goal of early referral and diagnosis. This includes also in secondary setting the appropriate use of imaging for making a diagnosis and the correct interpretation. Education about not using classification criteria for making a diagnosis is essential. The Berlin algorithm needs to be reviewed carefully, especially the dominant place of conventional radiographs can be challenged. Although MRI has also drawbacks; it can be discussed if in patients with chronic back pain (early phases of disease) that MRI might be more appropriate than conventional radiographs. Cost-effectiveness of both radiographs and MRI would be also an interesting topic to investigate.

PART II: THE USE OF IMAGING (MRI) IN EARLY AXIAL SPONDYLOARTHRITIS

Sacroiliitis is the hallmark of axSpA. Radiography is the most commonly used method to detect sacroiliitis, though patients may have symptoms years before abnormalities can be seen on radiography and it is therefore not very adequate in the detection of early disease. In addition, not all patients will develop structural bone damage in the axial skeleton. With the help of MRI, it became possible to visualize inflammatory changes., which usually become apparent much earlier in the disease course. As a consequence, non-radiographic axSpA is now a well-respected part of the disease spectrum.

In **chapter 4** results of a systematic literature review (SLR) are described which summarizes recent advances in both imaging modalities of sacroiliac joint imaging. It was concluded that substantial observer variation heavily influences reliability of conventional radiographs which leads to the fact that sacroiliitis is often missed or incorrectly diagnosed. This reader variability cannot be improved by training.[27] The poor reliability of evaluating conventional radiographs was established in post- hoc analyses on the data of the ABILITY-1 and RAPID-axSpA trials. More recent data from the DESIR cohort revealed that in recent onset IBP-patients, both trained readers and local rheumatologists/radiologists agree moderately in

recognizing radiographic sacroiliitis (kappa: 0.55- 0.54). A significant proportion of locally recognized AS patients was not confirmed by central reading (41.5% false-positives) while only a minority is false-negative (7.5%).[21]

In recent years, studies on MRI have been performed. ASAS developed useful recommendations how to perform an optimal MRI of the sacroiliac joints and developed a definition for a positive MRI.[28,29] MRI proved to be a more sensitive tool in the early detection of axSpA. In contrast to the moderate agreement regarding radiographic sacroiliitis, agreement regarding sacroiliitis on MRI was substantially better: as well between the two central readers in the DESIR cohort as between the local and central reader in this cohort (kappa: 0.73; kappa: 0.70 respectively).[20] In chapter 8 of this thesis, agreement on a positive MRI between the two readers was even better (kappa: 0.84).

With great interest; the effect of discrepant imaging reading was investigated on fulfilment of the ASAS axSpA classification criteria. Of the patients with discrepant MRI and/or radiograph reading; 28% could have been classified differently (sec looking at imaging) but only 7.9% were actually classified differently. This is mainly due to the presence of the clinical arm. In general; rheumatologists need to be aware of discrepant imaging data and this underlines the importance of reviewing a patient as a whole in the diagnostic process rather than to fully rely on imaging.

Due to the expanding literature, the question was raised whether the wording of the ASAS definition of a positive MRI was still appropriate. An often heard critical note in the field is that while reading an MRI one is tempted to simply count the visible white spots which will result in a low specificity.

Low specificity of the MRI finding of sacroiliac joint bone marrow edema may lead to misclassification, especially in populations with a low axSpA prevalence. In **chapter 5** a consensus exercise among experts in the field was undertaken. It was decided that the clear presence of bone marrow edema (BME) on MRI in subchondral bone is still considered to be the defining observation that determines the presence of active sacroiliitis though the presentation of the definition was reformatted and guidelines are provided essential to clinicians. It was emphasized that the definition is primarily for the classification of patients with SpA. In general, caution should be exercised in the interpretation of small lesions. Though detection of inflammation on a single slice may be sufficient for the criterion 'highly suggestive of SpA' it should be realised that it is rare for an MRI-SI with definite evidence of active sacroiliitis to demonstrate lesions on only a single image. MRI sequences (STIR, T1) should be simultaneously reviewed. If an inflammatory bone marrow lesion appears to be present, but it is hard to determine whether the lesion meets the criterion 'highly suggestive

of SpA' then the decision may be influenced by the presence of concomitant structural damage, especially erosion and/or other signs of inflammation, which in themselves do not suffice to meet the criterion.

As earlier mentioned, besides inflammatory lesions, structural lesions such as: erosions, fatty lesions, sclerosis and ankylosis are visible on MRI. Therefore, MRI has great potential for the assessment of both active inflammatory lesions and structural damage by means of one single-imaging technique. The ASAS group that developed the ASAS axSpA criteria abstained from including other lesions than bone marrow edema due to lack of evidence on the utility of structural lesions in the classification of axSpA. An important first step was to investigate the extent and performance of structural MRI-SI lesions in patients with suspected axSpA. Several studies have been performed on this topic, but since a control group was lacking it was impossible to assess the specificity of these lesions.[30-33] The study by de Hooge et al. *did* include a control group of CBP patients due to other causes than axSpA since these patients are included in the SPACE cohort. This made it possible to quantify MRI lesions in patients with and without axSpA. On purpose a high specificity (>95%) was selected to reduce misclassification of patients as the imaging arm is fulfilled in case of positive imaging plus only one additional SpA feature. This study revealed that the presence of at least five (≥5) fatty lesions and/or erosions as well as ≥3 fatty lesions and ≥3 erosions allowed an acceptable discrimination of axSpA and no SpA, while assuring >95% specificity.

These cut-offs were applied in two studies described in this thesis: **chapters 6 and 7**. In these studies, we wanted to further clarify the role of these structural lesions and to investigate their usefulness with regard to the ASAS axSpA classification of patients. Two scenarios were tested: the addition of structural lesions seen on MRI to the definition of 'sacroiliitis on imaging' (1) and the replacement of radiographic sacroiliitis by structural lesions on MRI (2). For both scenarios the impact on the classification of patients according to the ASAS axSpA criteria was assessed. It was investigated that while applying both scenarios; only minor changes in the ASAS axSpA classification took place. Most patients changed from one subcategory to another, rather than becoming ASAS axSpA positive or negative. Again, the clinical arm demonstrated its importance here. It was concluded that structural lesions on MRI can be used reliability either as an addition to or as a substitute for radiographs in the ASAS axSpA classification. This adds to the robustness of the ASAS axSpA criteria as a whole. Despite the fact that both replacement and addition had more or less the same effect (replacement was resulting in a loss of a small number of patients with a low likelihood of axSpA) for feasibility reasons we favour the scenario of addition.

We investigated the use of structural lesions with regard to classification. Though for diagnostic purposes; if a T1-sequence MRI is available in absence of a pelvic radiograph, this MRI may sometimes suffice if there are obvious abnormalities and in those circumstances there is no reason of obtaining additional radiographs. In the recently published European League Against Rheumatism (EULAR) recommendations for the use of imaging in the diagnosis and management of axSpA in clinical practice, it was also advocated to take structural lesions (such as bone erosion, fat infiltration, sclerosis and new bone formation) into account in addition to active inflammatory lesions and these data are in line with that.

As described earlier, the recognition of radiographic sacroiliitis is challenging. Unfortunately, agreement on structural lesions on MRI was only fair to moderate as well. It is however reassuring to see that the same conclusions (effects on ASAS axSpA classification) can be drawn while comparing the data of the individual readers. This strengthens our findings and adds to the validity of the criteria itself since the results seem not too much affected to inter-reader variation in this respect. This in contrast to the mNY criteria that immediately change in case of discrepant readings, as described earlier in this chapter.[21]

Because axSpA usually starts in the sacroiliac joints, active inflammatory (or structural) lesions of the *spine* were not incorporated in the ASAS axSpA classification criteria. However, we do know that inflammatory lesions in the spine occur in axial SpA,[34,35] sometimes even in the absence of sacroiliitis in MRI.[36] These studies raised interest to investigate the yield of a positive MRI-spine as imaging criterion in the ASAS axSpA classification of patients. On the basis of a literature review and expert consensus, the ASAS-OMERACT working group defined a positive (for active inflammation) MRI-spine in axSpA as the presence of ≥3 inflammatory lesions in the vertebrae; and the presence of each lesion on ≥2 consecutive slices.[33] Weber et al. advocated that the presence of ≥5 inflammatory lesions might discriminate even better from control groups[37] and the earlier described study by de Hooge et al. showed that a cut-off value of ≥5 inflammatory lesions defined a positive MRI-spine with a higher specificity of ≥95% (i.e. <5% patients without axSpA with a positive MRI-spine).

In SPACE and DESIR, the presence of a positive MRI-spine (using the cut-off of ≥5 inflammatory lesions) was investigated by Ez-Zaitouni et. al.[38] A positive MRI-spine was rarely seen in patients without sacroiliitis on MRI-SI and X-SI in both cohorts (SPACE: 1%, DESIR: 2% of the patients). Adding a positive MRI-spine as imaging criterion to the ASAS axSpA criteria, led to new classification in only one patient in each cohort as the other patients already fulfilled the clinical arm. Therefore, it was concluded that addition of MRI-spine as imaging criterion to the ASAS axSpA criteria had a low yield of newly classified patients and is therefore not recommended. However, involvement of the spine without sacroiliac joints can occur in a small percentage of patients and could be carefully considered during the

diagnostic process, especially in patients with longer symptom duration.

Although inflammation on MRI is now considered as an important manifestation in early axSpA, not much evidence was available on how inflammatory lesions develop over time (outside clinical trials). In **chapter 8** we investigated if it is useful to repeat an MRI of the sacroiliac joints after three months or one year in the diagnostic process of patients with chronic back pain suspected of axSpA in the SPACE cohort. Changes in MRI-SI status were seen in a minority of the patients of the SPACE cohort. Although changes were visible in both directions, more patients become negative than positive. And part of this becoming negative was associated with the start of TNF-blocking treatment. Repeating MRI after three months or one year in the diagnostic work-up in early disease is not useful. Both male gender and HLA-B27 positivity independently determine the likelihood of a positive MRI at any time point. This is in line with earlier studies.[39] Not unexpectedly, MRI status at baseline appeared to be strongly influencing the chance of having positive MRI of the sacroiliac joints at follow-up. If the baseline MRI is positive, the likelihood that the MRI will be positive again at three months or one year is very high (84%).

Future perspectives

A major unresolved challenge in imaging studies in axSpA is the selection of the external standard with which to compare MRI evaluation. Comparisons between different imaging modalities; for example linking structural lesions on MRI to low-dose CT will give us more insight. The availability of low-dose CT scans may help to increase the sensitivity of the imaging methods to detect the presence and progression of structural damage. Interesting future questions are how to incorporate MRI in future clinical trials and whether new drugs such as targeting the IL-23/IL-17 axis will have different effects on inflammation, fat deposition and other structural damage. Methodology is important here; because when we do not observe an effect of for example a biologic agent on radiographic progression this can be due to absence of effect; but also due to the fact we have not used the right measurement method. In general, prospective evaluation of both inflammatory and structural lesions over a sufficient timeframe is needed to further understand the development of axSpA lesions. Longitudinal data from the SPACE and DESIR cohort are awaited; but replication of our findings in cohorts of more advanced disease is also highly warranted. Ideally, in the near future a clinician can determine the risk of progression in an individual patient, using baseline parameters such as HLA-B27 positivity, radiographic structural damage, MRI-SIJ inflammation and elevated CRP and can fine-tune the treatment accordingly. Overall, regarding imaging in axSpA: optimal collaboration between rheumatologists and radiologists will be beneficial. The radiologist is the experienced imaging expert and the rheumatologist involved in the care of a given patient can place imaging findings in the context of clinical and laboratory data etc. Ideally,

clinical practice is a synergy between these two specialisms. Also, automated techniques for the evaluation of the volume, signal intensity, and extent of the relevant lesions are presently under development.

Although these approaches need to prove their ability to differentiate between pathologic lesions and local anatomic tissue abnormalities or artefacts to avoid false-positive or false-negative scoring results.

PART III: GENETIC ASPECTS IN EARLY AXIAL SPONDYLOARTHRITIS

Since the 1960s, it is known that susceptibility to AS is largely due to genetic factors.[40] HLA-B27 (a major histocompatibility class (MHC) class I molecule) is known to be the major genetic risk factor for AS.[41-43] The strong association with HLA-B27 was recognized over 40 years ago and since then it has undisputedly remained the strongest known risk factor. However, only 5-6% of the HLA-B27 positive people in the general population will develop spondyloarthritis[44] and the overall contribution of HLA-B27 to AS heritability is estimated at 23.3%.[45] This suggests that HLA-B27 by itself is not sufficient for development of the disease, supporting the contribution of additional genes. In other words, despite its strong association, HLA-B27 accounts for only a small *part* of the genetic risk of AS.

Within the MHC complex, HLA-B*4001 (an allele that corresponds to HLA-B60 at the serological or protein level) is identified to be another genetic risk factor for AS. HLA-B60 was shown to be increased in HLA-B27 positive AS patients in five independent data sets in 1989.[46] More recently, this association was confirmed in the UK, the Netherlands and in Taiwan.[47-49] In 2013, epistasis between HLA-B27 and HLA-B*4001 has been reported to associate with increased risk of AS in Caucasians, with a very high relative excess risk.[48] The epistatic interaction is not reproduced in all studies, but the high specificity of the combined genotype was found in all three previously mentioned studies (sensitivity: 10.1%, 18.2%, 18.7%, specificity: 99.7%, 99.6%, 98.7%).[48,49] In the study by van Gaalen et al. the combination of both HLA-B27 and HLA-B60 positivity was very rare in controls with a prevalence of just 0.4% while it was found in 18.2% of patients with AS.

The combined HLA-B27+/HLA-B*4001+ genotype has only been studied in advanced stage AS patients. The aim of this study is to assess the added value of HLA-B27/HLA-B*4001 in the detection of early axSpA. To our knowledge, no genetic studies have been earlier performed in early axSpA patients. For a disease where the genetic background is important, genetic testing could play a more prominent role in (early) diagnosis.

In **chapter 9** we assessed the prevalence of the HLA-B27+/HLA-B*4001+ genotype in two cohorts of patients with chronic or inflammatory back pain suspected of axSpA (SPACE and DESIR) and controls matched by country for both cohorts. The latter is relevant since the prevalence of HLA-B27 and HLA-B*4001 may differ by geographical location.[50] It was found that the high risk AS genotype (HLA-B27+/HLA-B*4001+) was significantly more common in both cohorts compared to controls (DESIR: 3.3%, SPACE: 4.8%, versus 0.4% in controls). Then we stratified patients by HLA-B typing (1. HLA-B27+/HLA-B*4001+; 2. HLA-B27+/HLA-B*4001-; 3. HLA-B27-/HLA-B*4001+; 4. HLA-B27-/HLA- B*4001-) and compared the disease characteristics among the different strata. HLA-B27+/HLA- B*4001+ patients showed a high percentage of radiographic sacroiliitis (DESIR 42% and SPACE 15% but were relatively similar to HLA-B27+/HLA-B*4001- back pain patients in terms of radiographic sacroiliitis (DESIR 27.6% and 16.5%) and to a lesser extent sacroiliitis on MRI. While comparing the *mean* number of SpA features (surrogate for an increased likelihood of axSpA) no differences were seen between HLA-B27+/HLA-B*4001+ (DESIR: 2.6, SPACE: 3) and HLA-B27+/HLA-B*4001- (DESIR: 2.7, SPACE: 3.2) patients. We concluded that the HLA-B27+/HLA-B*4001 high risk genotype was more common in early back pain patients suspected of axSpA. However, because HLA- B27+/HLA-B*4001+ patients were similar to HLA-B27+/HLA-B*4001- patients with regard to SpA features, combined testing for HLA-B27 and HLA-B*4001 has no added value in the early detection of axSpA.

Over the past decades, genetic technology in the field of AS has rapidly evolved. Several large genome-wide association studies (GWAS) have been carried out, leading to the discovery of many other genetic risk factors than HLA-B27 and HLA-B*4001.[51-54] With GWAS, a plethora of data is generated which may seem promising. However, many associations found account only for a small fraction of the risk of AS. Sample size is absolutely critical for the power of GWAS to detect associations reliably.

Another issue is the difficulty in identifying the effect on expression or function of a specific gene. Recently, two genetic loci have been associated with AS which might be of functional relevance: endoplasmic reticulum aminopeptidase (ERAP) and the interleukin (IL) 23 receptor.[52] ERAP encrypts an aminopeptidase expressed in the endoplasmic reticulum and is involved in preparing peptides for MHC class 1 presentation to immune effector cells. The IL-23 receptor activates T- helper cells secreting the cytokine interleukin (IL) 17, but as well other pro-inflammatory cells. The ERAP-1 association (not -2) is limited to HLA-B27 positive cases, expressing that peptides presented by HLA-B27 might be of importance.[55]

As described earlier in this thesis (Introduction) axSpA is clinically associated with inflammatory bowel disease (IBD), psoriasis or reactive arthritis in part of the patients. It has been shown that these diseases can be clinically silent,[56,57] therefore, the association with extra- articular

manifestations might be underestimated. Hence, barrier damage of dermal (psoriasis) and mucosal (IBD) surfaces (human host's barrier functions) and the subsequent exposure of the immune system to microbes seem to be an important aspect for the pathogenesis. Substantial overlap between AS susceptibility loci and IBD loci has been found. An altered microbiome has been found in IBD patients[58] and is thought to also play an important role in SpA.[59,60] Evidence that the gut microbiome is important in AS includes findings in several animal models of SpA.[61] In patients with microscopic bowel lesions, the disease probably starts in the gut, where IL-23 receptor- positive IL-17 and IL-22 producing innate lymphoid cells (ILCs) are activated perhaps through the gut microbiome. IL-17 is a pro-inflammatory cytokine, released by T-helper-17 cells on stimulation with IL-23. ILCs activated in the gut migrate to the entheses and joints, causing an inflammatory process in which TNF-a also participates. Recently, a metagenomics analysis was performed, comparing stool samples between adult SpA and control groups (both healthy controls and rheumatoid arthritis (RA)).[62] The results suggest that distinctive altered microbiomes characterise both SpA and RA. Furthermore, a reproducible increase in R. gnavus (an aerobic, Gram-positive gut microbe in the class of Clostridia) appears specific for SpA. This observation is consistent with the pro-inflammatory role of this bacteria and its association with IBD. It remains to be determined whether HLA-B27 influences the gut microbiome, but this has been suggested.

Future perspectives

Despite the progress that has been made, there is still a clear lack of understanding of pathogenesis in axSpA. The functional mechanisms of HLA-B27 and other genetic associations should be studied more thoroughly. Another topic for future research is the relation between cytokines, inflammation and bone formation. As described earlier, the interest in the role of the microbiome is expanding. This can be helpful to better understand the interaction between genetic predisposition and environment (exposure to microbes, bacterial triggers). Attention should also go to the possible influence of HLA-B27 on the gut microbiome. In general, improved animal models are warranted (TNF-dependent; ankylosing mouse models). Ideally we would link tissue samples to imaging to better understand the pathologies visualized by various imaging techniques although invasive techniques for obtaining tissue samples are undesirable. Furthermore, we are interested in the follow-up of axSpA patients from SPACE and DESIR in order to assess whether HLA-B*4001 and ERAP-1 are possible risk factors for disease progression (for example radiographic spinal progression; but also the progression of nr-axSpA to AS).

CONCLUDING REMARKS

To wrap-up at the end of this chapter; we stress the urge that the pathogenesis of axSpA needs to be unravelled to a larger extent in order to comprehend the exact mechanism and to investigate more possibilities to modify this (Part III). Likewise, the debate needs to continue as to whether and how classification and diagnosis can be improved; centred around the urge for early identification (Part I). The role of MRI in this process needs to be further specified (Part II); the course of both active and structural lesions over substantial follow-up periods will provide us with useful information and also the concordance with other imaging modalities (such as low-dose CT).

The studies in this thesis were all centred around the early recognition of axSpA. But of course, once the diagnosis has been made optimal treatment strategies are essential. Non-steroidal anti- inflammatory drugs and TNF blockers are effective therapies. But blockade of interleukin-17 is a relatively new and relevant treatment option and studies in nr-axSpA with anti-IL-17 therapy are awaited. Additional studies are still needed to evaluate TNF inhibitors plus NSAIDs with the aim to inhibit bone proliferation, as well as comparing biologics head-to-head in both biologic-naïve patients and those that fail to response to their first TNFi. Finally, a treatment that can stop radiographic progression remains an important unmet need.

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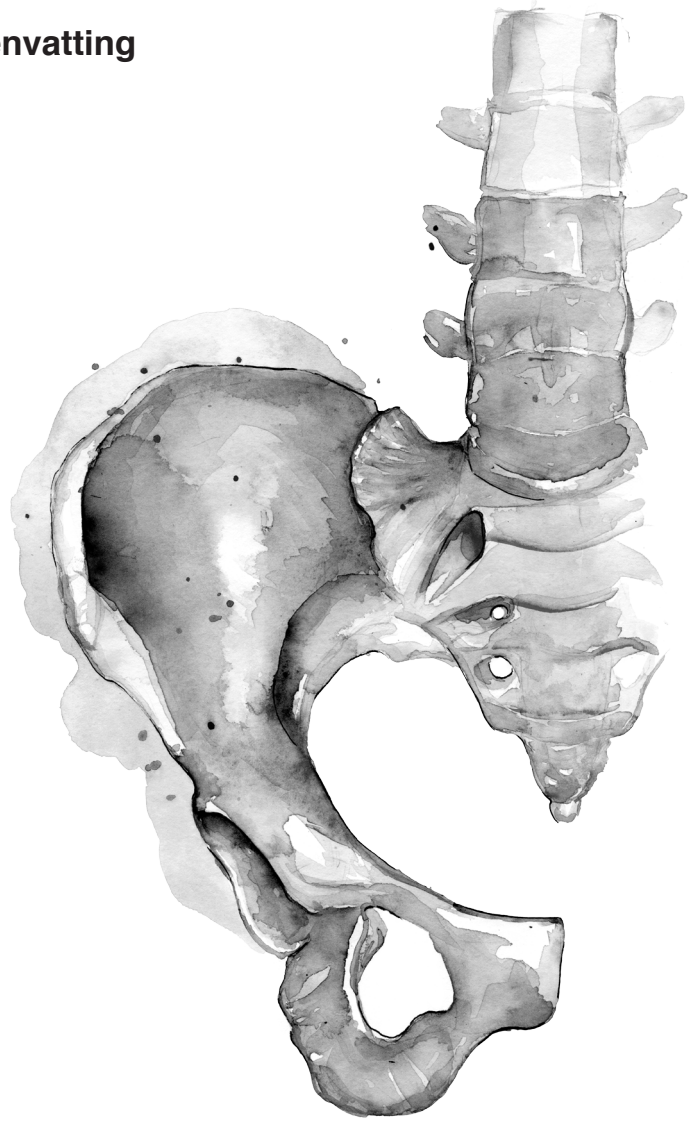
Nederlandse samenvatting



INTRODUCTIE

Spondyloartritis (SpA) is een chronische reumatische aandoening waarbij zowel gewrichten van de extremiteiten als de wervelkolom en het bekken betrokken kunnen zijn. Wanneer de ontstekingen met name gelokaliseerd zijn in de gewrichten die het bekken verbinden met de wervelkolom (de sacro-iliacale gewrichten) en/of de wervelkolom zelf spreekt men van axiale spondyloartritis (axSpA). Deze ontstekingen veroorzaken rugpijn en stijfheid en kunnen op termijn leiden tot ernstige verbening van de wervelkolom. Bij perifere spondyloartritis (pSpA) zijn juist de perifere gewrichten (bijvoorbeeld knieën en polsen) en pezen aangedaan. Het onderscheid tussen axSpA en pSpA is relatief nieuw in het veld. De voordelen van het kunnen maken van dit onderscheid voor het karakteriseren van patiënten met SpA zijn: een betere beschrijving van de gepresenteerde ziekte en een betere behandeling van de patiënt (aangezien de therapeutische strategieën anders zijn). De focus van dit proefschrift ligt vooral op axSpA.

De symptomen van axSpA zijn erg uiteenlopend. Er is helaas niet een eenduidig symptoom dat bij alle patiënten voorkomt. Wel zijn er symptomen die veel vaker voorkomen bij patiënten met axSpA dan bij patiënten met andere aandoeningen. Dit noemt men SpA kenmerken (SpA features). Een veelvoorkomend SpA kenmerk is inflammatoire rugpijn wat wordt vastgesteld aan de hand van de volgende symptomen: rugpijn die aanwezig is in rust, vermindering van rugpijn bij beweging, stijfheid van de rug in de ochtend gedurende meer dan 30 minuten, nachtelijke rugpijn en een alternerende pijn in de bilstreek. Naast ontstekingen van de perifere gewrichten (perifere artritis) kunnen peesaanhechtingen (entheses) ontstoken raken. Dit wordt gekenmerkt door een pijnlijke zwelling bijvoorbeeld ter plaatse van de aanhechting van de achillespees op het hielbeen. Ook kan een dactylitis optreden: hierbij is de gehele vinger of teen rood en ontstoken. Ontstekingen kunnen ook op andere plaatsen in het lichaam dan de gewrichten voorkomen: de zogenoemde extra-articulaire manifestaties. Hiermee worden bedoeld: ontstekingen aan de ogen (in de vorm van uveitis anterior), ontstekingen aan de huid (in de vorm van de huidaandoening psoriasis) en ontstekingen aan de darmen (in de vorm van inflammatoire darmziekten (IBD) zoals de ziekte van Crohn). Twee andere SpA kenmerken zijn het substantieel afnemen van pijn en stijfheid bij het gebruik van non-steroïdale anti-inflammatoire geneesmiddelen (NSAIDs) en een positieve familie anamnese welke is gedefinieerd als het voorkomen van de ziekte bij eerste-of tweedegraads bloedverwanten. Patiënten met axSpA hebben vaak verhoogde ontstekingswaarden in het bloed zoals een hoog CRP en/of een verhoogde bezinking. Aanwezigheid van het gen HLA-B27 (humaan leukocyten antigeen B27) wordt veel vaker gevonden in patiënten met axSpA.

De kenmerkende ontsteking van de sacro-iliacale (SI) gewrichten kan worden afgebeeld met röntgenonderzoek of magnetic resonance imaging (MRI). Sacroiliitis is het centrale kenmerk van axSpA. Een conventionele röntgenfoto is de meest gebruikte methode om sacroiliitis te detecteren. Het duurt echter vaak 6-8 jaar vanaf het begin van de symptomen voordat sacroiliitis op een conventionele röntgenfoto's kan worden vastgesteld. De gedachte is dat radiografische veranderingen (erosies, sclerose, vernauwing/verbreding van de gewrichtsspleet (ankylose) de latere gevolgen van de ontsteking weerspiegelen in plaats van de ontsteking zelf. Daarom is het niet erg geschikt voor de detectie van de ziekte in een vroeg stadium. Bovendien zullen niet alle patiënten uiteindelijk structurele laesies in het axiale skelet ontwikkelen.

Met behulp van MRI werd het mogelijk om inflammatoire veranderingen te visualiseren, die meestal veel eerder in het ziektebeloop zichtbaar worden. Als gevolg hiervan is niet-radiografische axSpA nu een gerespecteerd onderdeel van het ziektespectrum. Patiënten met axSpA kunnen dus worden geclassificeerd als één van de twee subtypes van axSpA: ankyloserende spondylitis (AS) of niet-radiografische axSpA (nr-axSpA). Patiënten met AS vertonen radiografische sacroiliitis. Dergelijke bevindingen zijn niet evident bij conventionele röntgenfoto's in nr-axSpA. In plaats daarvan is een bewijs van actieve ontsteking van de sacro-iliacale gewrichten op MRI essentieel.

Of en welke van de hierboven genoemde SpA kenmerken een patiënt heeft stelt een reumatoloog vast via anamnese, lichamelijk onderzoek, laboratoriumonderzoek en beeldvorming. Zo wordt een gedetailleerd klinisch beeld verkregen met als doel een passende diagnose te stellen. De waarschijnlijkheid van de diagnose varieert afhankelijk van de specifieke bevindingen die aanwezig zijn. De geschatte prevalentie van SpA in de algemene populatie is 1-1.4%, hoewel cijfers over de incidentie en prevalentie variëren en sterk afhankelijk zijn van methodologische verschillen tussen studies. Ongeveer 80% van de patiënten ontwikkelt de eerste symptomen op een leeftijd jonger dan 30 jaar (minder dan 5% van de patiënten is ten tijde van de eerste symptomen ouder dan 45 jaar). Lange tijd is gedacht dat axSpA vooral een ziekte was van (jongvolwassen) mannen. De aandoening komt echter ook bij vrouwen in ongeveer dezelfde frequentie voor.

AxSpA wordt geassocieerd met een aanzienlijke ziektelast. De uitkomsten van de ziekte in termen van verminderde mobiliteit, arbeidsproductiviteit en een slechtere gezondheidsgerelateerde kwaliteit van leven kunnen van grote invloed zijn op het leven van jonge patiënten. Het is daarom belangrijk om patiënten tijdig te identificeren om vroegtijdig te kunnen starten met behandeling en zo mogelijk het beloop van de ziekte te beïnvloeden.

Terwijl de behandeling van axSpA vroeger vooral bestond uit fysiotherapie en ontstekingsremmende pijnstillers (NSAIDs) is het therapeutische arsenaal in de afgelopen jaren snel uitgebreid. NSAID's zijn nog steeds de aanbevolen eerstelijns medicamenteuze behandeling voor patiënten met axSpA met pijn en stijfheid. Maar het tijdperk van TNF-blokkerende medicijnen en andere zogenaamde biologicals hebben een revolutie teweeg gebracht in de behandeling van axSpA patiënten die ongevoelig zijn voor eerstelijnsbehandeling en de resultaten zijn indrukwekkend.

Tijdige identificatie van patiënten heeft klinische consequenties en is dus relevant, maar helaas ook moeilijk. Het interval tussen het begin van de symptomen en de stellen van de diagnose bedraagt gemiddeld 8-10 jaar. AxSpA blijft een relatief ongebruikelijke oorzaak van een veel voorkomend eerste symptoom: 60-80% van de algemene bevolking rapporteert op enig moment in zijn/haar leven rugpijn. Ook speelt bijvoorbeeld de late schade op de röntgenfoto een rol. In het algemeen vormt de noodzaak tot een vroege herkenning van axSpA en het verkorten van de diagnostische vertraging de belangrijkste basis achter de verschillende onderdelen van dit proefschrift.

OPZET VAN DIT PROEFSCHRIFT

De studies beschreven in dit proefschrift zijn allemaal gecentreerd rondom hetzelfde doel: de vroege herkenning van axSpA en een verkorting van de vertraging in het diagnostische proces. Een belangrijke stap in het aanpakken van dit probleem was dat experts in het veld prospectieve cohort studies hebben ontworpen waarin opeenvolgende patiënten met chronische of inflammatoire rugpijn van korte duur worden geïncludeerd en vervolgd op een gestandaardiseerde manier met onder andere beeldvorming op gezette tijden. Dit stelt ons in staat om informatie te verkrijgen over wie axSpA zal ontwikkelen en wie niet. Deze cohort studies bieden waardevolle informatie over de vroege detectie en het ziektebeloop van axSpA en vormen de basis van het onderzoek gepresenteerd in dit proefschrift. Ook is een groot internationaal netwerk gericht op onderzoek naar axSpA opgericht; de Assessment of SpondyloArthritis international Society (ASAS).

Het eerste deel van dit proefschrift heeft betrekking op twee studies naar de prestaties van verschillende classificatiecriteria in een wereldwijde klinische setting en de noodzaak om aanvullend onderzoek uit te voeren (HLA-B27-testen; beeldvorming van de sacro-iliacale gewrichten) in een subgroep van patiënten met slechts één of zelfs nul SpA kenmerken: dat wil zeggen een lage voorafkans op axSpA. Vervolgens verschoof de focus naar de rol van beeldvorming in de vroege detectie van de ziekte. Eerst werd de literatuur over de recente vooruitgang in beeldvorming van de sacro-iliacale gewrichten (zowel

conventionele röntgenfoto's als MRI) besproken. Dit vormde gedeeltelijk het startpunt voor een consensusoefening die resulteerde in een update van de bestaande definitie voor een positieve MRI voor de classificatie van axSpA. Vervolgens werd de toegevoegde waarde van het gebruik van structurele laesies op MRI in de ASAS axSpA classificatiecriteria beoordeeld. Daarna zoomden we opnieuw in op het diagnostische proces; waarbij het nut van het herhalen van een MRI van de sacro-iliacale gewrichten (na drie maanden of een jaar) in patiënten met chronische rugpijn verdacht van axSpA werd geëvalueerd. In het laatste deel van dit proefschrift werd de prevalentie van het HLA-B27+/HLA-B*4001+ genotype beoordeeld in twee vroege axSpA cohorten; en de potentiële rol van dit genotype in de vroege opsporing van de ziekte.

De studies in dit proefschrift zijn uitgevoerd in twee prospectieve cohort studies en één studie met een cross-sectionele opzet (dwarsdoorsnede onderzoek). De twee cohort studies zijn het SPondyloArthritis Caught Early (SPACE) cohort and het DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort. SPACE is een doorlopend observationeel cohort onderzoek waarbij patiënten van 16 jaar en ouder met chronische rugpijn (≥3 maanden, ≤ 2 jaar en aanvang <45 jaar) verwezen naar een reumatoloog worden geïncludeerd en vervolgd. Patiënten worden gerekruteerd in verschillende centra in vier Europese landen: Nederland, Noorwegen, Italië en Zweden. De follow-up wordt op gestandaardiseerde wijze uitgevoerd: verzameling van klinische gegevens en beeldvorming op gezette tijdstippen (baseline, drie maanden, een jaar, twee jaar, daarna elke twee jaar). Basis- en één jaar follow-up gegevens werden gebruikt voor dit proefschrift. DESIR is een longitudinale cohort studie waarbij patiënten van 18-50 jaar met inflammatoire rugpijn (IBP) zijn opgenomen in 25 regionale centra in Frankrijk. De aanwezigheid van IBP en een duur van de rugpijn van ≥3 maanden en <3 jaar was vereist voor inclusie. Naast de verplichte aanwezigheid van IBP, werd een patiënt alleen opgenomen als de reumatoloog betrokken bij de inclusie van de patiënt van mening was dat de waarschijnlijkheid dat deze patiënt de diagnose axSpA heeft ten minste 50% was. Het cohort streeft naar een follow-up van 10 jaar, maar voor dit proefschrift werden alleen baseline gegevens gebruikt. Het SPACE cohort heeft belangrijke gelijkenissen met DESIR, hoewel een belangrijk verschil is dat bij DESIR alleen patiënten met IBP worden geïncludeerd, terwijl in SPACE de rugpijn niet noodzakelijkerwijs een inflammatoir karakter heeft. Bovendien is in DESIR de aanwezigheid van een axSpA-diagnose op zijn minst waarschijnlijk, terwijl dit niet het geval hoeft te zijn in SPACE. Een praktisch verschil is dat SPACE een doorlopend cohort onderzoek is; en DESIR een gesloten cohort studie (met inclusie tussen december 2007 en april 2010). De studie met het cross-sectionele ontwerp is de ASAS-COMOSPA studie. Dit is een door ASAS geïnitieerd onderzoek gericht op het evalueren van de prevalentie van comorbiditeiten en risicofactoren daarvoor bij patiënten met SpA (zowel axiaal als perifeer) in verschillende landen over de hele wereld. Het doel was

om brug te slaan tussen beschikbare aanbevelingen en de dagelijkse praktijk van de wijze waarop men met deze comorbiditeiten omgaat. Het is een internationaal, observationeel onderzoek waarin patiënten met de diagnose SpA (volgens de behandelende reumatoloog) werden opgenomen. Inclusie vond plaats in 22 landen uit vijf verschillende regio's over de hele wereld: Azië, Noord-Afrika, Latijns-Amerika, Noord-Amerika, Midden-Europa en West-Europa. De multi-nationaliteit en het grote aantal geïncludeerde patiënten, maakt het cohort ideaal voor het verrichten van aanvullende studies, zoals die beschreven in dit proefschrift.

DEEL I: VROEGE HERKENNING EN CLASSIFICATIECRITERIA

Aan de hand van de hierboven beschreven SpA kenmerken vormt de reumatoloog een zo gedetailleerd mogelijk klinisch beeld van de patiënt met als doel om tot een passende diagnose en behandeling te komen. Er bestaan geen strikte criteria voor het stellen van een diagnose en het diagnostische proces resulteert zodoende in heterogene groepen van patiënten. Om gedegen wetenschappelijk onderzoek te kunnen doen is het echter belangrijk om goed gedefinieerde homogene groepen te creëren voor patiënten die de diagnose axSpA hebben. Om dit te bereiken zijn verschillende sets van classificatiecriteria ontwikkeld. Hierbij worden aan de hand van overeenkomstige kenmerken patiënten in categorieën ondergebracht.

Eén van de meest bekende classificatiecriteria in het veld van axSpA zijn de in 1984 ontwikkelde modified New York (mNY) criteria. Deze criteria classificeren patiënten met ankyloserende spondylitis (AS) wat ook bekend staat als de ziekte van Bechterew. AS is de meest uitgesproken variant van axSpA en het wordt gekenmerkt door radiografische sacroiliitis. Radiografische sacroiliitis betreft structurele schade aan het bot, veroorzaakt door een ontsteking, vast te stellen middels röntgenfoto's van de sacro-iliacale (SI) gewrichten. Deze structurele schade wordt gegradeerd in ernst van graad 0 tot 4 per SI-gewricht. Radiografische sacroiliitis is in de mNY criteria gedefinieerd als graad ≥2 aan beide SI-gewrichten of graad 3-4 aan één van beide gewrichten. Echter, om aan de mNY-criteria te voldoen dient de patiënt naast radiografische sacroiliitis ook minimaal één van de volgende klinische kenmerken hebben: 1. lage rugpijn gedurende ten minste 3 maanden, die verbetert door beweging en niet door rust, 2. verminderde beweeglijkheid van de onderrug bij het zijwaarts buigen en bij naar voren en naar achteren buigen, 3. verminderd vermogen om de borstkas uit te zetten bij inademing vergeleken met de normaalwaarde voor geslacht en leeftijd.

De mNY-criteria behelzen axiale kenmerken van de ziekte en daarnaast een zeer beperkt aantal SpA kenmerken. Daarnaast geldt de eerder genoemde beperking van mogelijk absente röntgenologische afwijkingen bij vroege ziekte. Al met al hebben de beperkingen van de mNY-criteria geleid tot de ontwikkeling van de Amor-criteria en ESSG-criteria begin jaren negentig. In deze twee criteria sets zijn meer SpA kenmerken vertegenwoordigd en ze omvatten derhalve het hele SpA-spectrum.

De Amor-criteria bestaan uit een lijst met symptomen, die geen van alle noodzakelijk zijn om een patiënt als SpA te classificeren. Punten (1-3) worden toegewezen aan verschillende symptomen en in totaal zijn ten minste 6 punten nodig voor classificatie. In tegenstelling tot de Amor-criteria, worden voor de ESSG-criteria ingangscriteria gehanteerd door middel van verplichte aanwezigheid van inflammatoire rugpijn (IBP) of perifere artritis. Volgens de ESSG-criteria worden patiënten met ten minste één van de ingangscriteria in combinatie met één aanvullend criterium geclassificeerd als SpA.

De Amor- en ESSG-criteria omvatten het hele spectrum van SpA, maar ze kunnen axiale en perifere ziekte niet van elkaar onderscheiden. Daarnaast is de MRI niet opgenomen in deze criteria sets. In 2009 heeft een groep experts (verenigd in ASAS) twee nieuwe classificatiecriteria sets ontwikkeld: één voor axiale SpA (axSpA) en één voor perifere SpA (pSpA). Volgens de ASAS-classificatiecriteria voor axiale SpA (ASAS axSpA) kunnen de criteria worden toegepast wanneer een patiënt minimaal drie maanden chronische rugpijn heeft, met een aanvang voor het 45^{e} levensjaar. Een patiënt kan voldoen aan de ASAS axSpA criteria via (minimaal) één van de twee armen: de imaging arm (met de nadruk op beeldvorming) en/of de klinische arm (met de nadruk op HLA-B27 positiviteit). Patiënten voldoen aan classificatie via de imaging arm als één SpA kenmerk aanwezig is naast radiografische sacroiliitis (mNY-criteria) of actieve ontsteking op MRI suggestief voor sacroiliitis. Om te voldoen aan de klinische arm, moet de patiënt HLA-B27-positief zijn en ten minste twee andere SpA kenmerken hebben. De classificatiecriteria voor perifere SpA kunnen alleen worden toegepast bij patiënten met op dat moment perifere manifestaties. Om aan deze criteria te voldoen, moet een patiënt artritis, dactylitis of enthesitis hebben in combinatie met minstens één andere SpA kenmerk.

Classificatiecriteria worden vaak geëvalueerd in beperkte patiënten populaties, zoals cohort studies met strikte inclusiecriteria die patiënten includeren in gespecialiseerde klinieken. Dit leidt automatisch tot tamelijk homogene groepen patiënten en is essentieel voor het evalueren van de prestaties van die criteria en de proof-of-concept. Echter, het stelt tegelijkertijd de vraag hoe deze classificatiecriteria zouden presteren in een omgeving die sterk lijkt op de situatie in de dagelijkse klinische praktijk: een situatie waar een heterogene groep patiënten zich presenteert aan reumatologen in wereldwijde context.

Classificatiecriteria zijn allemaal ontwikkeld met behulp van 'expert opinion' als de externe standaard in de afwezigheid van een onbetwiste gouden standaard. Patroonherkenning vormt de basis van deze expert opinion: reumatologen combineren individuele patiëntkenmerken en symptomen met hun eigen kennis over het ziektepatroon (het zogenaamde 'Gestalt'). Het is daarom niet moeilijk te begrijpen dat 'expert opinion' geen eenduidig en homogeen concept is. Het kan mogelijk verschillende beelden van de ziekte integreren die nog beter te begrijpen zijn vanuit een mondiaal perspectief (diversiteit van patiënten populaties en reumatologie opleidingsprogramma's).

In **hoofdstuk 2** werden de prestaties van verschillende classificatiecriteria sets getest in een wereldwijde populatie van patiënten. Patiënten werden gerekruteerd uit de klinische praktijk van een groot aantal reumatologische centra over de hele wereld. We onderzochten of reumatologen wereldwijd een eenzelfde soort patiënten diagnosticeren met SpA, door te testen of patiënten aan dezelfde classificatie criteria voldeden. Dit werd gedaan in de veronderstelling dat aan hoe meer criteria een patiënt voldoet, des te groter de kans is dat een patiënt met de diagnose SpA ook echt SpA heeft. Geconcludeerd werd dat de meeste patiënten met een klinische diagnose van SpA aan verschillende classificatiecriteria voldeden en er een substantiële overlap was tussen de criteria, wat bijdraagt aan de geloofwaardigheid en validiteit van de criteria. In dit geval is het belangrijk om te vermelden dat dit cohort geen cohort is van vroege ziekte: 65% van de patiënten voldeed aan de mNY-criteria. Echter, ondanks de overlap tussen de criteria sets, werd een substantieel deel van de patiënten opgepikt door slechts één criteria set: namelijk de ASAS axiale SpA criteria.

De ASAS-criteria bleken beter te presteren dan classificatiecriteria sets zoals de Amor- en ESSG-criteria. De ASAS-criteria hebben met name een betere sensitiviteit door de aanwezigheid van MRI in de imaging arm. Wanneer getest tegenover de diagnose van experts, vertegenwoordigen de ASAS-criteria het huidige 'Gestalt' beter dan de ESSG- en AMOR-criteria, die tientallen jaren geleden zijn ontworpen vóór de introductie van MRI. Naast het feit dat MRI-bevindingen zijn opgenomen in de criteria, maken de ASAS-criteria onderscheid tussen axiale en perifere SpA. Hoewel de ESSG- en Amor-criteria het hele spectrum van SpA beslaan en een breder scala aan kenmerken bevatten in vergelijking met de modified New York-criteria, maken deze criteria géén onderscheid tussen axiale en perifere SpA. Deze differentiatie is echter wel belangrijk, bijvoorbeeld bij het testen van behandelstrategieën. Onlangs is een systematisch literatuuronderzoek en meta-analyse uitgevoerd om het bewijsmateriaal voor de prestaties van de ASAS-classificatiecriteria samen te vatten. De volledige set ASAS SpA-criteria leverden een hoge gepoolde sensitiviteit (73%) en specificiteit (88%) op. Evenzo werden goede resultaten gevonden voor de axSpA-criteria (sensitiviteit: 82%, specificiteit: 88%). Voor de andere criteria liggen deze getallen lager.

Niettemin hebben diverse reumatologen wereldwijd hun bezorgdheid geuit over de validiteit van de ASAS-criteria. Met name de specificiteit van de criteria staat ter discussie: de aanwezigheid van de klinische arm zou leiden tot een hogere sensitiviteit terwijl dit ten koste gaat van de specificiteit. Met andere woorden, patiënten die alleen voldoen aan de klinische arm, moeten niet worden beschouwd als 'echte' axSpA (mislabeling). Dit staat in schril contrast tot de imaging arm die breed erkend en geaccepteerd wordt. Daarom hebben we in hoofdstuk 2 de patiëntkarakteristieken vergeleken van patiënten die voldeden aan de klinische arm en de imaging arm. Er werd geconcludeerd dat patiënten die voldeden aan de klinische arm opvallend veel gelijkenissen hadden met patiënten die voldeden aan de imaging arm met betrekking tot de aanwezigheid van SpA kenmerken. Deze bevinding komt overeen met eerdere observaties in het SPACE cohort en het DESIR cohort. In de ABILITY-1-studie (een gerandomiseerde gecontroleerde studie die werd uitgevoerd om de werkzaamheid en veiligheid van adalimumab te beoordelen bij patiënten met non-radiografische axSpA) waren er ook geen opvallende verschillen tussen patiënten die aan de imaging arm en klinische arm voldeden. In deze studies werd ook opgemerkt dat patiënten in de verschillende armen niet alleen opvallend vergelijkbaar waren met betrekking tot de aanwezigheid van SpA kenmerken, maar ook met betrekking tot ziekteactiviteit (BASDAI en ASDAS). In de huidige ASAS-COMOSPA-studie werd de relevantie van de klinische arm opnieuw bevestigd.

Veel patiënten in dit onderzoek ondergingen geen MRI. Deze situatie is compatibel met de dagelijkse klinische praktijk aangezien MRI een relatief duur onderzoek is en de beschikbaarheid ervan soms beperkt. Als MRI niet beschikbaar is, blijft een aanzienlijk deel van de patiënten niet herkend en zal de sensitiviteit van de criteria afnemen. Mogelijk zal dit probleem groter zijn bij vrouwen, die een lager risico hebben op radiografische progressie (mannelijk geslacht was een risicofactor voor het ontwikkelen van radiografische sacroiliitis en dus voor de evolutie van nr-axSpA naar r-axSpA). Een ander belangrijk punt is het feit dat beeldvorming (zowel conventionele röntgenfoto's als MRI) moeilijk te interpreteren kan zijn in de klinische praktijk. In het DESIR cohort werd aangetoond dat zowel getrainde lezers als lokale reumatologen en radiologen slechts matig overeenkwamen voor de herkenning van sacroiliitis op röntgenfoto's. Een aanzienlijk deel van de patiënten die werden gelabeld als zijnde radiografische sacroiliitis door lokale lezers, werd niet bevestigd door centrale lezers (vals positief). In een ander onderzoek was onenigheid tussen lokale en centrale lezers over positieve radiografische sacroiliitis aanwezig bij 28% van de patiënten. Omdat beeldvorming vaker door lokale lezers als positief werd gemarkeerd, komt de specificiteit van de imaging arm in gevaar (fout-positiviteit). Zoals door onze studie werd aangetoond, voldoen veel patiënten aan zowel de imaging arm als de klinische arm. Daarom wordt het risico van de hierboven beschreven 'verkeerde interpretatie' minder prominent in de aanwezigheid van de

klinische arm. Ook dit onderstreept weer de relevantie van de klinische arm van de ASAS axSpA-criteria.

Tot voor kort was de validiteit van de ASAS-criteria alleen bestudeerd in een cross-sectionele setting: of iemand voldoet aan de classificatiecriteria, en of iemand de diagnose heeft volgens de reumatoloog (externe standaard) wordt op hetzelfde moment bekeken. In zekere zin zijn de begrippen sensitiviteit en specificiteit statische begrippen, die los staan van predictieve eigenschappen. Het is van essentieel belang om te weten of patiënten die aanvankelijk werden geclassificeerd als axSpA nog steeds worden beschouwd als patiënten met een SpA-diagnose na jarenlange follow-up. Onlangs zijn er gegevens over de voorspellende validiteit van de ASAS-criteria gepubliceerd: patiënten uit het ASAS cohort werden gedurende 3-5 jaar gevolgd en reumatologen hebben de patiënten daarna opnieuw bekeken. 93.3% van de patiënten die aanvankelijk aan de criteria voldeden, zou nog steeds worden gediagnosticeerd als axSpA door de reumatoloog. Dit leidt tot een uitstekende voorspellende waarde en suggereert eveneens consistentie van de criteria over de tijd. Vergelijkbare resultaten werden gevonden voor de imaging arm (range: 94.5-96.5%) en klinische arm (range: 96.4-98.2%) en ook voor patiënten die alleen aan de imaging arm voldeden (bereik: 85.1-86.7%) ofwel alleen aan de klinische arm (bereik: 87.9-92.9%). De negatief voorspellende waarde was iets lager. Echter, omdat het bekend is dat SpA kenmerken in de loop van de tijd kunnen veranderen zou dit wellicht het natuurlijke ziektebeloop kunnen reflecteren in plaats van een negatieve test karakteristiek. Omdat vergelijkbare positief voorspellende waardes voor beide armen van de axSpA-criteria werden gevonden, ondersteunen deze gegevens ook de opvatting dat de klinische arm een groep patiënten omvat die evenzeer tot het SpA-spectrum behoort als de patiënten die aan de imaging arm voldoen.

Door het ontbreken van diagnostische criteria kunnen artsen in de verleiding komen om classificatiecriteria als zodanig te gebruiken. Dezelfde klinische- laboratorium- en beeldvorming-gegevens worden gebruikt voor classificatie en diagnose, maar er bestaan duidelijke verschillen in de toepassing ervan. Voorzichtigheid is geboden bij het gebruik van classificatiecriteria als lijstjes met kenmerken die kunnen worden aangevinkt om een diagnose te stellen. Een essentiële stap die gemist wordt door eenvoudig SpA kenmerken te tellen, is de uitsluiting van andere waarschijnlijke diagnoses (differentiaal diagnostisch denken) en negatieve bevindingen die niet in de richting van axSpA wijzen. Zoals eerder uitgelegd, zijn de criteria ontworpen voor classificatie in plaats van diagnostische doeleinden en moeten ze alleen worden toegepast bij patiënten met de diagnose SpA (en niet omgekeerd). Het probleem van het gebruik van classificatiecriteria om een diagnose te stellen, is met name problematisch bij patiënten die niet worden gezien door een reumatoloog en vooral als de pre-testkans laag is. Bij patiënten met een relatief hoge pre-test probabiliteit zoals in de studies uit dit proefschrift, waar de pre-test waarschijnlijkheid rond de 30% is, is dit risico minder groot.

Bovendien werd in SPACE uitsluiting van andere waarschijnlijke diagnoses door de reumatoloog uitgevoerd nog voordat patiënten werden geïncludeerd in SPACE (formeel exclusie criterium). Daarnaast werd de evaluatie van SpA kenmerken alleen door experts gedaan. Classificatiecriteria zijn ontwikkeld om een duidelijk ja/nee-antwoord te krijgen, waarmee een vrij homogene groep patiënten wordt gecreëerd, meestal voor opname in een cohort studie of klinische trial. Ze zorgen voor vergelijkbaarheid tussen deze studies, maar het is moeilijk om het volledige scala van ziektebeelden te vangen aan de hand van een reeks criteria. Zoals hierboven uitgelegd, is kennis van de pre-test probabiliteit van het hebben van de ziekte essentieel in de diagnose. In een cohort van patiënten met chronische rugpijn bij een huisarts in de eerstelijns gezondheidszorg, werd SpA gediagnosticeerd in 5% van de gevallen en dit wordt vaak gebruikt als de veronderstelde pre-test probabiliteit van deze ziekte. In de studies beschreven in dit proefschrift hebben we de 5% pre-test waarschijnlijkheid gebruikt om bijvoorbeeld likelihood ratios te berekenen. Maar gezien onze studies zijn uitgevoerd in een secundaire dan wel tertiaire setting, waarbij de vooraf kans dat patiënten axSpA hebben groter is dan in de eerstelijnszorg is dit waarschijnlijk een conservatieve schatting. Helaas was een schatting van de pre-test probabiliteit in deze setting onbekend toen het cohort werd gestart, maar na een paar jaar hebben we geconstateerd dat het ongeveer 30% is. De pre-test waarschijnlijkheid van 5%, die we gebruikten, resulteerde dus in een onderschatting van de waarschijnlijkheid van post-test ziekte.

De diagnostische work-up van axSpA is een uitdaging; enkele van de argumenten waarom dit het geval is zijn de revue al gepasseerd. In het algemeen moet de ziekte worden vermoed bij patiënten met chronische rugpijn (chronic back pain: CBP) met een aanvang vóór het 45e levensjaar en een voorgeschiedenis van CBP die bijna drie maanden of langer continu aanwezig is (sub-acuut begin). Dit zou moeten leiden tot verdere evaluatie om vast te stellen of andere SpA kenmerken aanwezig zijn. Het gemodificeerde Berlijn algoritme dient als een nuttig hulpmiddel om reumatologen te helpen bij de diagnose van axSpA. Het algoritme suggereert dat röntgenfoto's van de sacro-iliacale gewrichten worden aanbevolen bij alle verwezen patiënten met rugpijn met de hierboven beschreven kenmerken, ongeacht de aanwezigheid van andere SpA kenmerken. Indien negatief worden alle patiënten beoordeeld op de aanwezigheid van andere SpA kenmerken en getest voor HLA-B27. In het onderzoek beschreven in **hoofdstuk 3** hebben we geprobeerd te onderzoeken of HLA-B27 testen en beeldvorming van de sacro-iliacale gewrichten (door middel van conventionele röntgenfoto's en MRI) noodzakelijk is in een subgroep van patiënten met een lage voorafkans op axSpA: gedefinieerd als patiënten met nul of slechts één SpA kenmerk na klinisch onderzoek en meting van acute fase eiwitten in het laboratoriumonderzoek. Verrassend genoeg werd een diagnose axSpA gesteld in 18.4% van de patiënten met nul SpA kenmerken en 17.9% van de patiënten met één SpA kenmerk. We waren verrast door deze relatief hoge percentages.

Zelfs bij patiënten zonder één enkel SpA kenmerk na klinisch onderzoek en meting van acute fase eiwitten was het niet mogelijk om axSpA volledig uit te sluiten. Het is belangrijk om rekening te houden met de populatie van patiënten waarin de onderzoeksvraag werd onderzocht. Patiënten die deel uitmaken van het SPACE cohort worden doorverwezen naar een reumatoloog. Bepaalde red flags of andere bevindingen kunnen tot deze verwijzing hebben geleid. En in feite zijn meer waarschijnlijke diagnoses al uitgesloten. Daarom moeten de resultaten van deze studie niet worden geëxtrapoleerd of gegeneraliseerd naar bijvoorbeeld de huisartsenpraktijk.

Deze nuances terzijde gelegd, is het verrassend dat in deze groepen van patiënten met een lage voorafkans op SpA de diagnose niet zo ongewoon is als vooraf werd ingeschat. Het kan worden betwijfeld hoe realistisch de meerderheid van deze diagnoses is. Beeldvorming speelt een cruciale rol en is vaak doorslaggevend bij het al dan niet stellen van een diagnose. Dit is goed te begrijpen, aangezien radiologische afwijkingen aanvoelen als een objectief teken van ziekte. Maar ter illustratie voelt het onjuist dat bij een vrouwelijke patiënt met rugpijn zonder enig ander SpA kenmerk de diagnose wordt gesteld op basis van de solitaire vaststelling van sacroiliitis op röntgenfoto's. Aan de andere kant kan een diagnose nog steeds te rechtvaardigen zijn vanwege kenmerken of symptomen die buiten de formele SpA kenmerken vallen en dus buiten de kenmerken die we hebben geëvalueerd, bijvoorbeeld aanwezigheid van structurele laesies op een MRI van de sacro-iliacale gewrichten (MRI-SI) of inflammatoire laesies. Het kan ook zijn dat het gemodificeerde algoritme van Berlijn strikt wordt opgevolgd, met name door minder ervaren reumatologen (in opleiding) op het gebied van axSpA. Er moet nogmaals worden benadrukt dat het gemodificeerde Berlijn algoritme alleen een hulpmiddel is bij het stellen van een diagnose en dat het differentiaal diagnostisch denken hier niet door vervangen mag worden. Ook staat de dominantie van conventionele röntgenfoto's in het gemodificeerde Berlijn algoritme ter discussie. In het algemeen is er debat gaande in hoeverre aanvullende onderzoeken moeten worden uitgevoerd om een diagnose goed te keuren ofwel af te wijzen en er zijn zorgen geuit als de huidige diagnostische work-up niet al te uitgebreid is, vooral bij patiënten met een lage pre-test probabiliteit. Idealiter zouden we een diagnostisch proces op maat willen, waarbij artsen alleen specifieke onderzoeken onder bepaalde motivaties moeten uitvoeren. Bovendien zal alleen de langdurige follow-up van deze patiënten bevestigen of de diagnose correct is geweest en ook is het interessant om progressie van afwijkende bevindingen op de beeldvorming over tijd te vervolgen.

Sequentieel testen wordt ook bepleit in het gemodificeerde Berlijn algoritme. Hoewel we het algoritme formeel niet hebben getest in hoofdstuk 3, denken we dat de rol voor een MRI van de sacro-iliacale gewrichten (MRI-SI) misschien wat te beperkt is. MRI-SI zou alleen in een zeer specifieke situatie moeten worden uitgevoerd. Dit in scherp contrast met de conventionele röntgenfoto, wat de breed erkende eerste stap van het algoritme is. In een groep patiënten

met klachten van korte duur zoals het SPACE cohort is het echter zeer waarschijnlijk dat radiografische veranderingen nog niet zijn opgetreden wat tot vals-negatieve diagnoses zou kunnen leiden als er geen andere tests worden uitgevoerd. De onlangs gepubliceerde EULAR-aanbevelingen zijn eveneens minder conservatief en bevelen MRI-SI aan als een alternatieve eerste methode bij beeldvorming van bijvoorbeeld jonge patiënten met een korte symptoomduur. In het later beschreven hoofdstuk 8 zullen we het verloop van MRI-SI-activiteit over een jaar en de identificatie van voorspellende factoren voor een positieve MRI evalueren.

Toekomstperspectieven

De vroege diagnose van axSpA door een reumatoloog is belangrijk en een hoofddoelstelling van dit proefschrift. Echter de identificatie van patiënten met een verhoogd risico op axSpA in de eerste lijn is hiervoor essentieel. Het is evident dat een late verwijzing van patiënten naar een reumatoloog bijdraagt aan de diagnostische vertraging. Chronische rugpijn komt veel voor in de algemene populatie maar in de eerste lijn is axSpA in slechts 5% van de gevallen de oorzaak. Effectieve verwijsstrategieën zijn hierbij zeer belangrijk. Daarvoor is een verhoogd bewustzijn van de ziekte van cruciaal belang, op niveau van dokter en patiënt. Onderwijs is belangrijk om het doel van vroege verwijzing en diagnose te bereiken. Dit omvat ook bij tweedelijns instellingen het juiste gebruik van beeldvorming en een correcte interpretatie hiervan. Vooral dat laatste is zeer relevant, op dit moment vindt nationale voorlichting ook plaats. Voorlichting over het niet gebruiken van classificatiecriteria voor het stellen van een diagnose is essentieel. Het algoritme van Berlijn moet zorgvuldig worden herzien, vooral de dominante plaats van conventionele röntgenfoto's staat ter discussie. Hoewel MRI ook nadelen heeft lijkt het in het traject van vroege diagnose meer geschikt dan conventionele röntgenfoto's. In dit licht zou het ook interessant zijn om de kosteneffectiviteit van zowel conventionele röntgenfoto's als MRI te onderzoeken.

DEEL II: HET GEBRUIK VAN BEELDVORMING (MRI) IN VROEGE AXIALE SPONDYLOARTRITIS

In **hoofdstuk 4** worden de resultaten van een systematische literatuurstudie (systematic literature review, SLR) beschreven die recente vorderingen in het onderzoek naar beide beeldvormende modaliteiten van de sacro-iliacale gewrichten (conventionele röntgenfoto's en MRI) op een rij zetten. Geconcludeerd werd dat substantiële verschillen in de beoordeling van conventionele röntgenfoto's de betrouwbaarheid van dit onderzoek sterk beïnvloeden, wat ertoe leidt dat sacroiliitis vaak wordt gemist of ten onrechte wordt vastgesteld. Deze variabiliteit in beoordeling tussen lezers (zowel reumatologen als radiologen) kon helaas

niet worden verbeterd door training van de lezers. De slechte betrouwbaarheid van het evalueren van conventionele röntgenfoto's werd ook gesignaleerd in post-hoc analyses van de ABILITY-1 en RAPID axSpA-trials. Meer recente gegevens van het DESIR cohort lieten zien dat bij patiënten met inflammatoire rugpijn verdacht voor axSpA zowel getrainde lezers als lokale reumatologen en radiologen het gematigd eens waren over de herkenning van radiografische sacroiliitis. Een aanzienlijk deel van de lokaal erkende patiënten werd niet bevestigd door centrale lezing (41.5% fout-positieven) terwijl slechts een minderheid fout-negatief was (7.5%).

In de afgelopen jaren zijn veel studies op het gebied van MRI uitgevoerd. ASAS ontwikkelde nuttige aanbevelingen voor het uitvoeren van een optimale MRI van de sacro-iliacale gewrichten en ontwikkelde ook een definitie voor een positieve MRI. In tegenstelling tot de gematigde overeenkomst met betrekking tot radiografische sacroiliitis was de overeenstemming over sacroiliitis op MRI aanzienlijk beter: zowel tussen de twee centrale lezers in het DESIR cohort als tussen de lokale en centrale lezer in dit cohort. In hoofdstuk 8 van dit proefschrift was overeenstemming over een positieve MRI tussen de twee lezers zelfs nog beter (kappa: 0.84).

Het effect van discrepantie van de beeldvorming werd onderzocht op basis van de ASAS axSpA classificatiecriteria. Van de patiënten met een afwijkende MRI en/of röntgenfoto had 28% had anders kunnen worden geclassificeerd (sec op beeldvorming), maar slechts 7.9% was ook daadwerkelijk anders geclassificeerd. Dit komt voornamelijk door de aanwezigheid van de klinische arm. In het algemeen dienen reumatologen zich bewust te zijn van de mogelijke discrepanties ten aanzien van beeldvorming. Dit onderstreept in het diagnostische proces het belang van het beoordelen van een patiënt als geheel in plaats van volledig te vertrouwen op beeldvorming.

Vanwege de expansieve toename in literatuur op dit gebied werd de vraag gesteld of de formulering van de ASAS definitie van een positieve MRI nog steeds de juiste was. Een vaak gehoorde kritische opmerking in het veld is dat tijdens het lezen van een MRI men in de verleiding komt om gewoon de zichtbare witte vlekken te tellen op de STIR sequenties, wat resulteert in een lage specificiteit (dat wil zeggen: dat veel gezonde proefpersonen wel de uitslag krijgen van een afwijkende MRI omdat beenmergoedeem ook een aspecifiek teken kan zijn, fout-positiviteit). Een lage specificiteit van de MRI-bevinding van beenmergoedeem kenmerkend voor sacroiliitis kan leiden tot misclassificatie, vooral bij patiëntpopulaties met een lage axSpA-prevalentie.

In **hoofdstuk 5** werd een consensusoefening onder deskundigen op dit gebied verricht. Er werd besloten dat de duidelijke aanwezigheid van beenmergoedeem (bone marrow edema, BME) op MRI in subchondraal bot nog steeds wordt beschouwd als de bepalende waarneming die de aanwezigheid van actieve sacroiliitis bepaalt, hoewel de presentatie van de definitie opnieuw werd geformatteerd. Er werd benadrukt dat de definitie primair is voor de *classificatie* van patiënten met SpA. Verder werd toegevoegd dat voorzichtigheid is geboden bij de interpretatie van kleine laesies. Hoewel detectie van ontsteking op een enkele slice voldoende kan zijn voor het criterium 'zeer suggestief voor SpA' moet worden gerealiseerd dat het zeldzaam is voor een MRI-SI met duidelijk bewijs van actieve sacroiliitis om slechts laesies aan te tonen op één enkele afbeelding. MRI-sequenties (STIR, T1) moeten tegelijkertijd worden beoordeeld. Als er een inflammatoire beenmerglaesie lijkt te bestaan, maar het is moeilijk om te bepalen of de laesie voldoet aan het criterium 'zeer suggestief voor SpA', werd gesteld dat de beslissing kan worden beïnvloed door de aanwezigheid van bijkomende structurele schade. Structurele schade is het best zichtbaar op de T1-sequentie (tezamen te beoordelen met de STIR-sequentie) en omvat bijvoorbeeld erosies, die op zichzelf niet voldoende zijn om aan het criterium te voldoen maar wél een ondersteunende bijdrage kunnen hebben. Dat structurele laesies op zich niet voldoende zijn voor een positieve MRI heeft niet zozeer te maken met de mogelijk beperkte aanvullende waarde van deze laesies (dit wordt juist wel zo verondersteld) maar op dit moment is er nog te weinig evidence om deze laesies formeel bij de definitie te betrekken. Dit wordt echter wel binnen afzienbare termijn verwacht. Al met al hebben de huidige wijzigingen al wel geleid tot een belangrijke specificatie van een positieve MRI voor sacroiliitis.

Het voorkomen en de evolutie van structurele laesies in patiënten met axSpA is een hot topic. Naast erosies kunnen ook vervetting, sclerose en ankylose worden waargenomen. Daarom heeft MRI een groot potentieel voor de beoordeling van zowel actieve inflammatoire laesies als structurele schade door middel van één enkele beeldvormende techniek. De ASAS-groep die de ASAS axSpA-criteria ontwikkelde, onthield zich van het opnemen van andere laesies dan beenmergoedeem vanwege een gebrek aan bewijs over het nut van structurele laesies in de classificatie van axSpA. Een belangrijke eerste stap was het onderzoeken van de omvang en prestaties van structurele laesies op MRI-SI bij patiënten met vermoedelijk axSpA. Er zijn verschillende studies uitgevoerd, maar aangezien een controlegroep ontbrak, was het onmogelijk om de specificiteit van deze laesies te bepalen.

De studie van *de Hooge* et al. heeft wel een controlegroep van CBP-patiënten opgenomen aangezien deze patiënten zijn opgenomen in het SPACE cohort. Dit maakte het mogelijk om MRI-laesies te kwantificeren bij patiënten met en zonder axSpA. Met opzet werd een hoge specificiteit (>95%) geselecteerd om misclassificatie van patiënten te voorkómen, aangezien wordt voldaan aan de imaging arm bij positieve beeldvorming plus slechts één extra SpA

kenmerk. Deze studie toonde aan dat de aanwezigheid van minstens vijf (≥5) vettige laesies en/of erosies evenals ≥3 vettige laesies en ≥3 erosies een aanvaardbare discriminatie van axSpA en geen SpA mogelijk maakte terwijl een> 95% specificiteit werd gegarandeerd.

Deze afkappunten hebben wij toegepast in twee studies beschreven in dit proefschrift: **hoofdstuk 6 en hoofdstuk 7**. In deze studies wilden we de rol van deze structurele laesies verder verduidelijken en hun bruikbaarheid met betrekking tot de ASAS axSpA classificatie van patiënten onderzoeken. Twee scenario's werden getest: het *toevoegen* van structurele laesies op MRI aan de definitie van 'sacroiliitis op de beeldvorming' (1) en het *vervangen* van radiografische sacroiliitis door structurele laesies op MRI (2). Voor beide scenario's werd de impact op de ASAS axSpA classificatie van patiënten geïnventariseerd. Gevonden werd dat bij het toepassen van beide scenario's slechts kleine wijzigingen in de ASAS axSpA-classificatie optraden. De meeste patiënten veranderden van de ene subcategorie naar de andere, in plaats van dat de classificatie an sich veranderde (van ASAS axSpA positief naar negatief of vice versa). Het belang van de aanwezigheid van de klinische arm wordt hier nogmaals onderschreven. Er werd geconcludeerd dat structurele laesies op MRI betrouwbaar kunnen worden gebruikt als een toevoeging aan of als vervanging voor röntgenfoto's in de ASAS axSpA-classificatie. Dit draagt bij aan de robuustheid van de ASAS axSpA-criteria als geheel. Ondanks het feit dat zowel vervanging als toevoeging min of meer hetzelfde effect hadden (vervanging leidde tot verlies van een klein aantal patiënten met een lage waarschijnlijkheid van axiale SpA) geven we de voorkeur aan het scenario van toevoeging. Dit om redenen van praktische uitvoerbaarheid.

We hebben het gebruik van structurele laesies met betrekking tot de ASAS axSpA classificatie onderzocht. Echter, als voor diagnostische doeleinden een T1-sequentie beschikbaar is in afwezigheid van een conventionele röntgenfoto én er zijn duidelijke afwijkingen is er in dat geval geen reden om alsnog extra röntgenfoto's te laten maken. In de onlangs gepubliceerde aanbevelingen van de EUropean League Against Rheumatism (EULAR) voor het gebruik van beeldvorming bij de diagnose en het beleid van axSpA in de klinische praktijk, werd ook gepleit om te kijken naar de aanwezigheid van structurele laesies (zoals erosies, vetinfiltratie, sclerose en nieuwe botvorming) naast actieve inflammatoire laesies. Onze gegevens komen daarmee overeen.

Zoals eerder beschreven, is de herkenning van radiografische sacroiliitis een uitdaging. Helaas was de overeenstemming over structurele laesies op MRI nog steeds slechts matig tot redelijk. Het is echter geruststellend om te zien dat dezelfde conclusies (effecten op ASAS axSpA classificatie) kunnen worden getrokken door de gegevens van de individuele lezers te vergelijken. Dit versterkt onze bevindingen en draagt bij aan de validiteit van de criteria zelf, omdat de resultaten niet te veel worden beïnvloed voor de variatie tussen de

lezers op dit punt. Dit in tegenstelling tot de modified New York-criteria die onmiddellijk veranderen in het geval van discrepante metingen en met ook een veranderende ASAS axSpA classificatie tot gevolg.

Omdat axiale SpA gewoonlijk begint in de sacro-iliacale gewrichten, zijn actieve inflammatoire (of structurele) laesies van de wervelkolom niet opgenomen in de ASAS axSpA classificatie criteria. We weten echter dat inflammatoire laesies in de wervelkolom optreden in axiale SpA: soms zelfs bij afwezigheid van sacroiliitis in MRI, zoals aangetoond in de eerder beschreven ABILITY-1 trial. Deze studies hebben belangstelling gewekt voor het onderzoeken van de opbrengst van een positieve MRI-wervelkolom als beeldvormingscriterium in de ASAS axSpA-classificatie van patiënten. Op basis van een literatuurstudie en consensus van deskundigen, heeft de ASAS-OMERACT werkgroep een positieve MRI-wervelkolom in axSpA gedefinieerd als de aanwezigheid van ≥ 3 inflammatoire laesies in de wervels; en de aanwezigheid van elke laesie op ≥2 opeenvolgende slices. De Canadese groep van *Weber* et al. pleitte ervoor dat de aanwezigheid van ≥5 inflammatoire laesies nog beter zou kunnen discrimineren tussen axSpA-patiënten en controlegroepen. Ook de eerder beschreven studie van *de Hooge* et al. toonde aan dat een afkapwaarde van ≥5 inflammatoire laesies een positieve MRI-wervelkolom definieerde met een hoge specificiteit van ≥95% (d.w.z. <5% patiënten zonder axSpA met een positieve MRI van de wervelkolom).

In SPACE en DESIR werd de aanwezigheid van een positieve MRI-wervelkolom (met behulp van de cut-off van ≥ 5 inflammatoire laesies) onderzocht door onze onderzoeksgroep (Ez-Zaitouni et al.). Hieruit is gebleken dat een positieve MRI-wervelkolom zelden werd gezien bij patiënten zonder sacroiliitis op MRI-SI en conventionele röntgenfoto's in zowel SPACE (1%) als DESIR (2%). Het toevoegen van een positieve MRI-wervelkolom aan de imaging arm van de ASAS axSpA-criteria, leidde tot een andere classificatie in slechts één patiënt per cohort, o.a. gezien deze patiënten vaak ook aan de klinische arm voldeden. Daarom werd geconcludeerd dat toevoeging van MRI-wervelkolom als beeldvormingscriterium aan de ASAS axSpA-criteria niet wordt aanbevolen. De betrokkenheid van de wervelkolom zonder sacro-iliacale gewrichten kan echter bij een klein percentage van de patiënten optreden en kan tijdens het diagnostisch proces zorgvuldig worden mee genomen, vooral bij patiënten met een langere symptoomduur.

In termen van diagnose kan bij sommige patiënten een langere periode van follow-up en monitoring nodig zijn, inclusief aanvullend beeldonderzoek. Hoewel inflammatie op MRI nu wordt beschouwd als een belangrijke manifestatie in vroege axSpA, was er niet veel bewijs beschikbaar over hoe inflammatoire laesies zich ontwikkelen over de tijd. In **hoofdstuk 8** hebben we onderzocht of het in het kader van het diagnostische proces zinvol is om na drie maanden of een jaar een MRI van de sacro-iliacale gewrichten te herhalen bij patiënten

met chronische rugpijn met verdenking op axSpA. Geconcludeerd werd dat veranderingen in de MRI-SI-status werden waargenomen bij slechts een minderheid van de patiënten in het SPACE cohort. Hoewel veranderingen in beide richtingen zichtbaar waren, werden meer patiënten negatief dan positief over de tijd. En een deel van dit negatief worden was geassocieerd met het begin van de behandeling met TNF-blokkade. Het herhalen van MRI na drie maanden of een jaar in het diagnostisch onderzoek bij vroege ziekte bleek niet zinvol. Gevonden werd dat zowel het mannelijke geslacht als de HLA-B27-positiviteit onafhankelijk van elkaar de waarschijnlijkheid op een positieve MRI beïnvloeden (op elk moment). Niet onverwacht leek de MRI-status bij baseline de kans op positieve MRI van de sacro-iliacale gewrichten bij de follow-up sterk te beïnvloeden. Als de baseline MRI positief is, is de kans dat de MRI opnieuw positief zal zijn na drie maanden of een jaar erg hoog (84%).

Toekomstperspectieven

Een belangrijke onopgeloste uitdaging in beeldvormingsstudies in axSpA is de selectie van de externe standaard waarmee de MRI kan worden vergeleken. Vergelijkingen tussen verschillende beeldvormingsmodaliteiten; bijvoorbeeld het koppelen van structurele laesies op MRI aan een low-dose CT zal ons meer inzicht verschaffen. De beschikbaarheid van low-dose CT kan de gevoeligheid van de beeldvormingsmethoden verhogen door de aanwezigheid en progressie van structurele schade te detecteren en deze gegevens te koppelen. Interessante toekomstige vragen zijn hoe MRI kan worden opgenomen in toekomstige klinische onderzoeken en of nieuwe geneesmiddelen zoals het aangrijpen op de IL-23/IL-17-as verschillende effecten zullen hebben op ontsteking en het ontwikkelen van structurele laesies. Methodologie is hier belangrijk, omdat vanzelfsprekend -als we geen effect van bijvoorbeeld een biologisch agens op radiografische progressie waarnemen- dit kan worden veroorzaakt door afwezigheid van effect; maar ook vanwege het feit dat we niet de juiste meetmethode hebben gebruikt. In het algemeen is prospectieve evaluatie van zowel inflammatoire als structurele laesies gedurende een voldoende lange tijd nodig om de ontwikkeling van axSpA-laesies verder te begrijpen. Longitudinale gegevens van het SPACE- en DESIR cohort worden verwacht, maar replicatie van onze bevindingen in cohorten van meer geavanceerde ziekte zijn ook zeer gewenst. Idealiter kan een clinicus in de nabije toekomst het risico van progressie bij een individuele patiënt bepalen, met behulp van baseline parameters zoals HLA-B27-positiviteit, radiografische structurele schade, inflammatie op MRI-SI, verhoogd CRP en kan de behandeling dienovereenkomstig worden verfijnd. Ten aanzien van beeldvorming in axSpA is een optimale samenwerking tussen reumatologen en radiologen van groot belang. De radioloog is de ervaren expert op het gebied van beeldvorming en de reumatoloog die betrokken is bij de zorg van een bepaalde patiënt kan de bevindingen plaatsen in een klinische context. Idealiter is in de klinische praktijk sprake van een synergie tussen deze twee medisch specialismen. Een

andere interessante ontwikkeling is dat op dit moment veel onderzoek wordt gedaan naar geautomatiseerde technieken voor de evaluatie van het volume, de signaalintensiteit en de omvang van de relevante laesies. Hoewel deze benaderingen hun vermogen nog moeten aantonen om onderscheid te maken tussen pathologische laesies en lokale anatomische weefselafwijkingen of artefacten (om vals-positieve of fout-negatieve scoringsresultaten te voorkómen) wordt van deze technieken veel verwacht.

DEEL III: GENETICA IN VROEGE AXIALE SPONDYLOARTRITIS

Sinds de jaren zestig is bekend dat genetische factoren een grote rol spelen bij AS. Het eerder genoemde HLA-B27 (een major histocompatibility class (MHC) I molecuul) staat bekend als de belangrijkste genetische risicofactor. De sterke associatie met HLA-B27 werd meer dan 40 jaar geleden erkend en is sindsdien de sterkste bekende risicofactor gebleven. Slechts 5-6% van de HLA-B27-positieve mensen in de algemene bevolking zal de ziekte ontwikkelen en de totale bijdrage van HLA-B27 aan de erfelijkheid van AS wordt geschat op 23.3%. Dit suggereert dat HLA-B27 alléén niet voldoende is voor de ontwikkeling van de ziekte en dit ondersteunt de bijdrage van andere genen. Met andere woorden, ondanks de sterke associatie is HLA-B27 slechts verantwoordelijk voor een klein deel van het totale genetische risico van AS.

Binnen het MHC-complex is HLA-B*4001 (een allel dat overeenkomt met HLA-B60 op serologisch of eiwit-niveau) geïdentificeerd als een tweede genetische risicofactor voor AS. In 1989 is in vijf onafhankelijke cohorten aangetoond dat HLA-B60 toegenomen was in HLA-B27 positieve AS-patiënten. Recent werd deze associatie bevestigd in een drietal cohorten in het Verenigd Koninkrijk, Nederland en Taiwan, respectievelijk. In 2013 werd gevonden dat epistasie (de interactie tussen genen op verschillende loci) tussen HLA-B27 en HLA-B*4001 verband houdt met een verhoogd risico op AS bij Kaukasiërs, met een zeer hoog overmatig risico. De epistatische interactie is niet in alle onderzoeken gereproduceerd, maar de hoge specificiteit van het gecombineerde genotype werd wél gevonden in alle drie eerder genoemde studies (sensitiviteit: 10.1%, 18.2%, 18.7%, specificiteit: 99.7%, 99.6%, 98.7%). In het onderzoek van van Gaalen et al. bleek de combinatie van zowel HLA-B27 als HLA-B60-positiviteit zeer zeldzaam bij controles met een prevalentie van slechts 0.4%, terwijl deze werd gevonden bij 18.2% van de patiënten met AS.

Het gecombineerde HLA-B27+/HLA-B*4001+ genotype is alleen bestudeerd in patiënten met ankyloserende spondylitis (AS) in een vergevorderd ziekte stadium. Het doel van studie in dit proefschrift was om de toegevoegde waarde van HLA-B27/HLA-B*4001 in de detectie van vroege axSpA te beoordelen. Voor zover wij weten, zijn er geen eerdere genetische studies uitgevoerd bij vroege axSpA-patiënten. Voor een ziekte waarbij de genetische achtergrond belangrijk is, zouden genetische testen een prominentere rol kunnen spelen in de opsporing van de ziekte. In **hoofdstuk 9** hebben we de prevalentie van het HLA-B27+/HLA-B*4001+ genotype bekeken in twee cohorten van patiënten (SPACE en DESIR) met chronische of inflammatoire rugpijn verdacht van axSpA en controles gerangschikt per land voor beide cohorten. Dit laatste is relevant omdat de prevalentie van HLA-B27 en HLA-B*4001 per geografische locatie kan verschillen. Er werd gevonden dat het AS-type met hoog risico (HLA-B27+/HLA-B*4001+) significant vaker voorkwam in beide cohorten vergeleken met de controles (DESIR: 3.3%, SPACE: 4.8%, versus 0.4% in controles). Vervolgens stratificeerden we de patiënten door HLA-B-typering (1. HLA-B27+/HLA-B*4001+; 2. HLA-B27+/HLA-B*4001-; 3. HLA-B27-/HLA-B*4001+; 4. HLA-B27-/HLA-B*4001-) en vergeleken we de ziektekenmerken tussen de verschillende strata. HLA-B27+/HLA-B*4001+ patiënten vertoonden een hoog percentage radiografische sacroiliitis (DESIR 42% en SPACE 15%) maar waren relatief vergelijkbaar met HLA-B27+/HLA-B*4001- rugpijnpatiënten (DESIR 27.6% en 16.5%) en in mindere mate sacroiliitis op MRI. Wanneer het gemiddeld aanwezige aantal SpA kenmerken (surrogaat voor een verhoogde kans op axiale SpA) werd vergeleken werden geen verschillen waargenomen tussen HLA-B27+/HLA-B*4001+ (DESIR: 2.6, SPACE: 3) en HLA-B27+/HLA-B*4001- (DESIR: 2.7, SPACE: 3.2) patiënten. We concludeerden derhalve dat het HLA-B27+/HLA-B*4001 hoogrisico genotype weliswaar vaker voorkwam bij patiënten met vroege rugpijn verdacht van axSpA, maar dat gecombineerd testen voor HLA-B27 en HLA-B*4001 geen toegevoegde waarde heeft in de vroege detectie van axSpA.

In de afgelopen decennia is de genetische technologie op het gebied van AS snel geëvolueerd. Verschillende grote genoom-brede associatiestudies (genome-wide association studies, GWAS) zijn uitgevoerd, wat heeft geleid tot de ontdekking van vele ándere genetische risicofactoren dan HLA-B27 en HLA-B*4001. Met GWAS wordt een veelheid aan gegevens gegenereerd die veelbelovend lijken. Echter, veel gevonden associaties zijn slechts verantwoordelijk voor een klein deel van het risico op AS. De grootte van de steekproef (omvang) is absoluut cruciaal voor het vermogen van GWAS om koppelingen betrouwbaar te detecteren. Een ander probleem is de moeilijkheid om het effect op expressie of functie van een specifiek gen te identificeren. Onlangs zijn twee genetische loci in verband gebracht met AS, die van functionele relevantie kunnen zijn: endoplasmatisch reticulum-aminopeptidase (ERAP) en de interleukine (IL) 23-receptor. ERAP codeert een aminopeptidase wat tot expressie wordt gebracht in het endoplasmatisch reticulum en is

betrokken bij het voorbereiden van peptiden voor presentatie van MHC klasse 1 aan immuun-effectorcellen. De IL-23-receptor activeert T-helpercellen die het cytokine-interleukine (IL) 17 en andere pro-inflammatoire cellen uitscheiden. De ERAP-1-associatie (niet -2) is beperkt tot HLA-B27-positieve gevallen, wat tot uitdrukking brengt dat peptiden die door HLA-B27 gepresenteerd worden van belang kunnen zijn.

Zoals eerder in dit proefschrift beschreven is axSpA bij een deel van de patiënten klinisch geassocieerd met inflammatoire darmaandoeningen (IBD), psoriasis of reactieve artritis. Het is aangetoond dat deze ziekten niet altijd tot klinisch evidente verschijnselen leiden: daarom kan de associatie met extra-articulaire manifestaties worden onderschat. Een beschadigde barrière van de mucosale oppervlakken van de huid (psoriasis) en darm (IBD) en de daaropvolgende blootstelling van het immuunsysteem aan micro-organismen lijkt een belangrijke rol te spelen in de pathofysiologie. In diermodellen is aangetoond dat het veranderde microbioom van de darm belangrijk is in AS. Echter, dit is grotendeels nog een onontgonnen onderzoeksveld.

Toekomstperspectieven

Ondanks de vooruitgang die is geboekt, is er nog steeds een duidelijk gebrek aan begrip van pathogenese in axSpA. De functionele mechanismen van HLA-B27 en andere genetische associaties moeten grondiger worden bestudeerd. Een ander onderwerp voor toekomstig onderzoek is de relatie tussen pro-inflammatoire cytokines, ontsteking en botvorming. De mechanismen waardoor botontsteking en erosies kunnen optreden bij patiënten met axSpA samen met nieuwe botvorming zijn nog niet volledig opgehelderd. In relatie tot andere reumatologische aandoeningen is dit een uniek en nog grotendeels onbegrepen fenomeen. Idealiter zouden we weefselmonsters koppelen aan beeldvorming om de pathogene processen beter te begrijpen die gevisualiseerd worden door verschillende beeldvormingstechnieken. Zoals eerder beschreven, breidt de belangstelling voor de rol van het microbioom zich uit. Dit kan nuttig zijn om de interactie tussen genetische aanleg en omgeving (blootstelling aan microben, bacteriële triggers) beter te begrijpen. Ook interessant is de mogelijke invloed van HLA-B27 op het microbioom. Verder zijn we geïnteresseerd in de follow-up van axSpA-patiënten van SPACE en DESIR om te beoordelen of HLA-B*4001 en ERAP-1 mogelijke risicofactoren zijn voor ziekteprogressie (bijvoorbeeld radiografische spinale progressie en syndesmofytvorming) maar ook voor bijvoorbeeld de progressie van nr-axSpA naar AS).

TOT SLOT

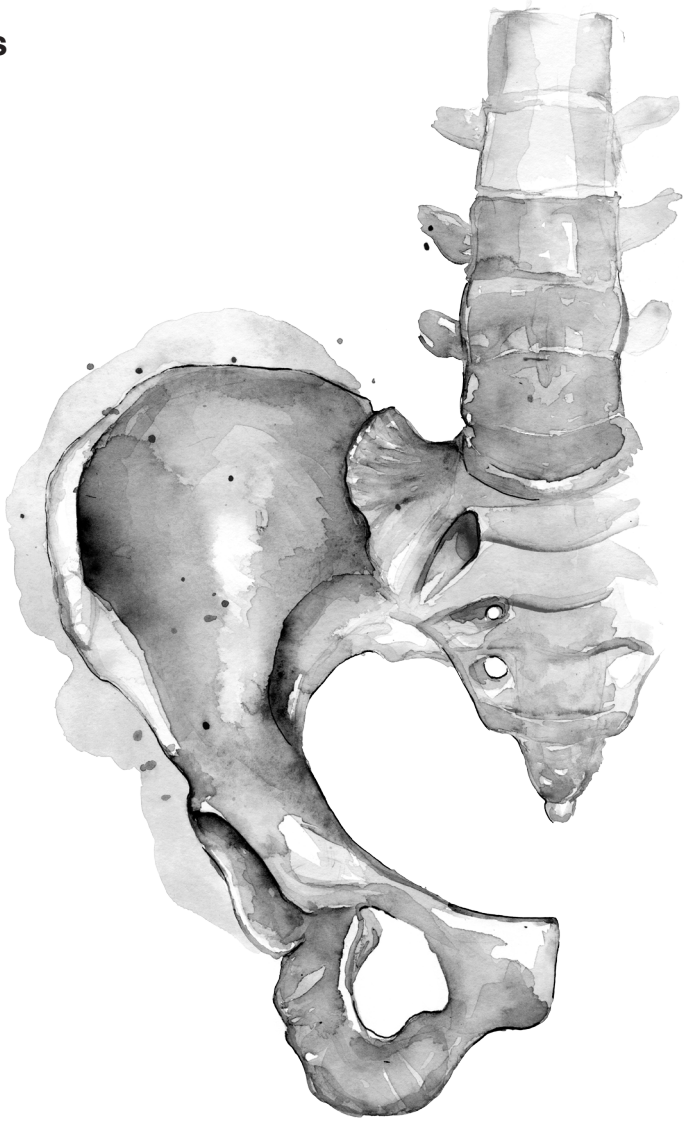
We onderschrijven nogmaals het belang dat de pathogenese van axSpA nader wordt opgehelderd. Meer van de genen die betrokken zijn bij de pathogenese dienen te worden geïdentificeerd, maar vooral moeten de functionele mechanismes van de bekende genetische associaties duidelijker worden. Idealiter vinden we hiermee aangrijpingspunten om met behandeling nog gerichter te interveniëren (deel III). Evenzo moet het debat worden voortgezet over de vraag of en hoe classificatie en diagnose kunnen worden verbeterd bij de vroege identificatie van axSpA patiënten (deel I). MRI zal hierbij een belangrijke rol spelen (deel II) en het verloop van zowel actieve als structurele laesies over langere tijd zal ons zinvolle informatie verschaffen. Ook de overeenstemming met andere modaliteiten (zoals de low-dose CT) is relevant. De studies in dit proefschrift zijn allen gecentreerd rondom de vroege herkenning van axSpA, maar wanneer de diagnose eenmaal is gesteld zijn optimale behandelstrategieën essentieel. Treat-to-target door het meten van ziekte activiteit en het zo nodig aanpassen van de behandeling resulteert in een verbetering van uitkomsten waarbij het doel is om klinische remissie te bereiken. Een belangrijke onbeantwoorde onderzoeksvraag is of behandeling ook daadwerkelijk leidt tot preventie of vertraging van de ontwikkeling van structurele schade. Idealiter is het binnen niet afzienbare tijd mogelijk om botproliferatie en radiografische progressie te stoppen. Hopelijk wordt dit bereikt in het onderzoeksveld indien wij, net als onze axSpA patiënten, ook zelf blijven bewegen.

11

List of publications

Curriculum vitae

Dankwoord



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CURRICULUM VITAE

Pauline Bakker werd geboren op 24 juni 1986 in Rotterdam. In 2004 behaalde zij haar VWO diploma aan het Sint Laurenscollege in Rotterdam waarna zij startte met de studie Geneeskunde aan de Universiteit Leiden. Tijdens haar studie was ze een aantal jaren als student-lid verbonden aan de Opleidingscommissie Geneeskunde van het Leids Universitair Medisch Centrum (LUMC). In 2007 deed ze een klinische stage Kindergeneeskunde in het Komfo Anokye Teaching Hospital in Kumasi in Ghana. In 2008-2009 onderbrak zij haar studie voor een full-time bestuursfunctie van de Medische Faculteit der Leidse Studenten (M.F.L.S.). Ook was ze dat jaar als vice-voorzitter van de Organizing Committee van de Leiden International Medical Student Conference (LIMSC) verantwoordelijk voor het wetenschappelijke programma van dit grote internationale studentencongres. Voor aanvang van de coschappen werd zeven maanden basaal wetenschappelijk onderzoek verricht aan het Imperial College in Londen naar de rol van specifieke T-cellen en NK-cellen bij de pathogenese van reumatoïde artritis. Na het behalen van het artsexamen in augustus 2012 *(cum laude)* ging zij in maart 2013 als arts-onderzoeker aan de slag op de afdeling Reumatologie van het LUMC onder begeleiding van prof. dr. D.M.F.M. van der Heijde, dr. F.A. van Gaalen en dr. M. Reijnierse. De resultaten van het onderzoek zijn beschreven in dit proefschrift. Aldaar coördineerde zij tevens een aantal klinische trials op het gebied van axiale spondyloartritis en gaf zij onderwijs aan studenten Geneeskunde. Na de aanvankelijke gedachte zich te specialiseren in de Interne Geneeskunde, koos zij met volle overtuiging voor de Oncologie en specifieker de Radiotherapie als latere werkveld. Per 1 september 2016 is zij werkzaam als arts-assistent in opleiding tot radiotherapeut-oncoloog in het LUMC (opleiders: prof. dr. C.A.M. Marijnen, prof. dr. C.L Creutzberg). Onderdeel hiervan was een stage Interne Geneeskunde in het Groene Hart Ziekenhuis in Gouda (opleider: dr. T. Koster). Per oktober 2018 zal een deel van de opleiding worden gevolgd in het Haaglanden Medisch Centrum (HMC) in Den Haag (opleiders: dr. R. Wiggenraad, dr. A. Verbeek-de Kanter).

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